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MONSANTO RESEARCH CORPORATION
BOSTON LABORATORIES
Everett 49, Massachusetts

Contracts No. DA-18-108-405-CML-807
DA-18-108-CML-6632

FINAL REPORT

Covering the Period
1 June 1960 to 31 May 1962

SYNTHESIS OF 5-ALKYLRESORCINOLS

Prepared by

Stanley D. Koch
James L. Dever
Paul F. Donovan

31 May 1962

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FOREWORD

This is the Final Report on U. S. Army Contracts No. DA-18-108-405-CML-807 and No. DA-18-108-CML-6632 by the Monsanto Research Corporation. The work was sponsored by the Chemical Research Division, U. S. Army Chemical Research and Development Laboratories, Army Chemical Center. Mr. Donald H. Wadsworth and Dr. Friedrich W. Hoffmann were the Project Officers.

Dr. Stanley D. Koch was the Project Leader for the Monsanto Research Corporation. Most of the work was done by Mr. James L. Dever and Mr. Paul F. Donovan, chemists, and Peter S. Simone, technician. Some of the early work on the Wittig route was done by Dr. John E. Harris, Sr. Catalytic hydrogenations and large-scale syntheses were carried out by Dr. Morton H. Gollis, group leader, Dr. Asher A. Hyatt, chemist, and Mr. James P. Brogna, Mr. Michael L. Cook, Mr. Henry L. Smith, and Mr. William A. Wicks, technicians. Instrumental analyses were carried out by Mr. Benjamin J. Gudzinowicz, group leader, Mrs. Jeanette C. Alm, Mrs. Ann E. Bekebrede, Mrs. Shirley A. Liebman, Mr. William R. Smith, and Mr. Maurice H. Taylor, chemists, and Mr. Conrad A. Cenerizio, technician. Elemental analyses were performed by Dr. Carol K. Fitz, Needham Heights, Massachusetts.

SUMMARY

A number of synthetic routes to 2-(3,5-dihydroxyphenyl)-3-methyloctane have been investigated. The most practical route starts from 1,3,5-trichlorobenzene, which is converted in two steps to 3,5-dimethoxyphenylmagnesium chloride. This Grignard reagent is reacted with 2-methylheptanonitrile, and the resulting ketone is reacted with methylmagnesium halide to give 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2. This carbinol is dehydrated, reduced, and cleaved to produce the desired resorcinol.

A large number of other routes and variations in individual steps were also investigated and detailed comparisons of their merits are included.

The synthesis of six related alkylresorcinols was also investigated. Two of these were prepared: 2-(3,5-dihydroxyphenyl)-3,4-dimethyloctane and 2-(3,5-dihydroxyphenyl)-3,3-dimethyloctane. A key precursor for three of the others was prepared.

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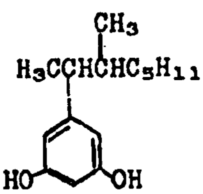
I. INTRODUCTION

This work has been directed toward better methods of synthesis of 2-(3,5-dihydroxyphenyl)-3-methyloctane (I) from readily available starting materials, and toward preparation of small samples of six related resorcinols: 2-(3,5-dihydroxyphenyl)-3,4-dimethyloctane (II), 2-(3,5-dihydroxyphenyl)-2,3-dimethyloctane (III), 2-(3,5-dihydroxyphenyl)-3,3-dimethyloctane (IV), 2-(3,5-dihydroxyphenyl)-2,3,3-trimethyloctane (V), 2-(3,5-dihydroxyphenyl)-2-methylhexane (VI), and 2-(3,5-dihydroxyphenyl)-2-methylheptane (VII).



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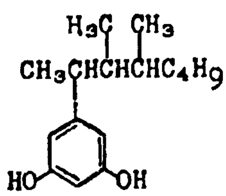

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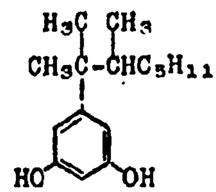

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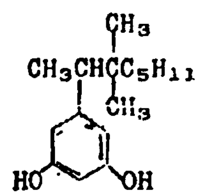

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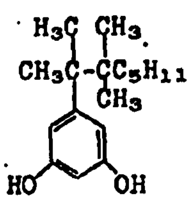

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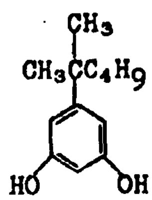

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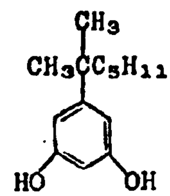
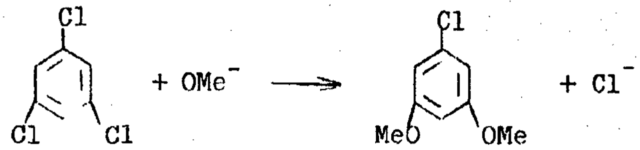


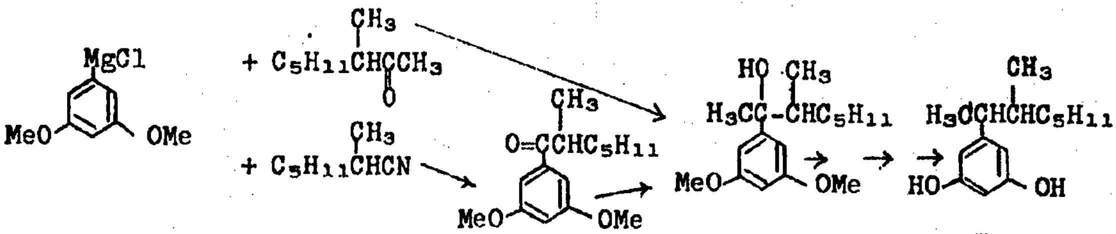
VII

A. GRIGNARD ROUTES TO RESORCINOL I

The Grignard routes are all based on 1-chloro-3,5-dimethoxybenzene as a key intermediate. Seven routes to this chloride have been considered. The most economical and practical is the methanolysis of 1,3,5-trichlorobenzene.



1-Chloro-3,5-dimethoxybenzene is then converted to its Grignard reagent, and this can be reacted with either 3-methyloctanone-2 or 2-methylheptanonitrile to proceed to the desired product.



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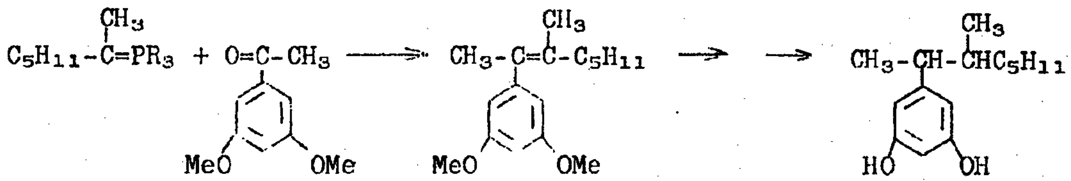
This work has shown the reaction with 2-methylheptanonitrile to be the more practical. This conclusion is supported by a great deal of development work on the route via 3-methyloctanone-2.

B. OTHER ROUTES TO RESORCINOL I

Five other approaches, with variations and ramifications, were also investigated as possible routes to resorcinol I. All were either unsuccessful or very much less practical than the Grignard routes. The key reaction in each of the routes is shown:

The Wittig route:



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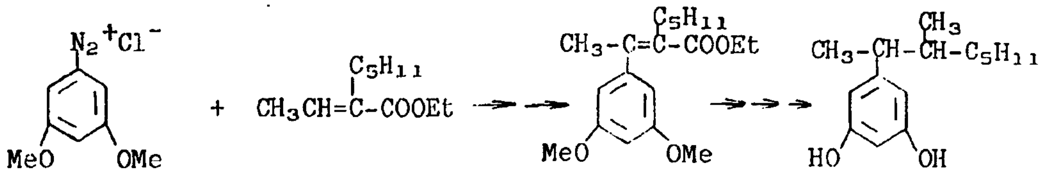
The Meerwein reaction route (arylation of olefins):



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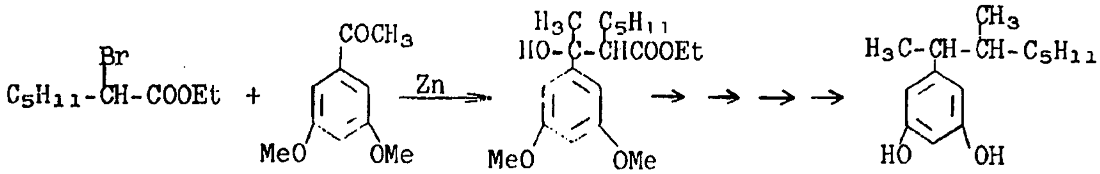
The Reformatsky reaction route:



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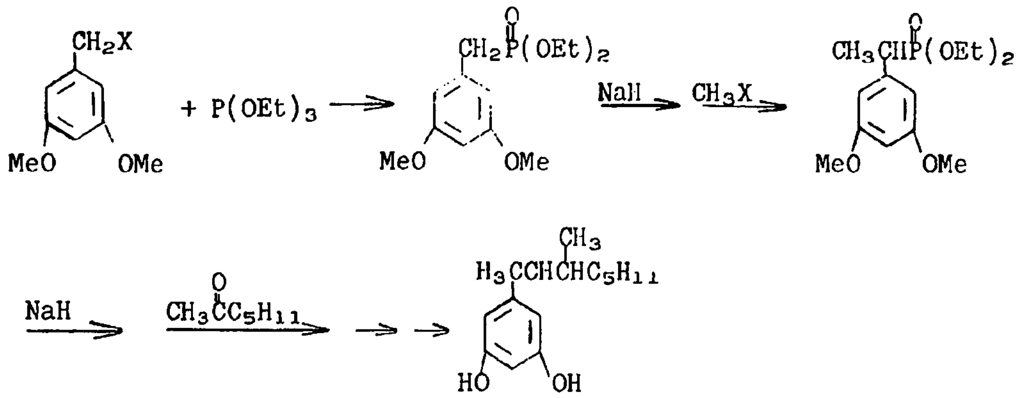
The phosphonate carbanion route:



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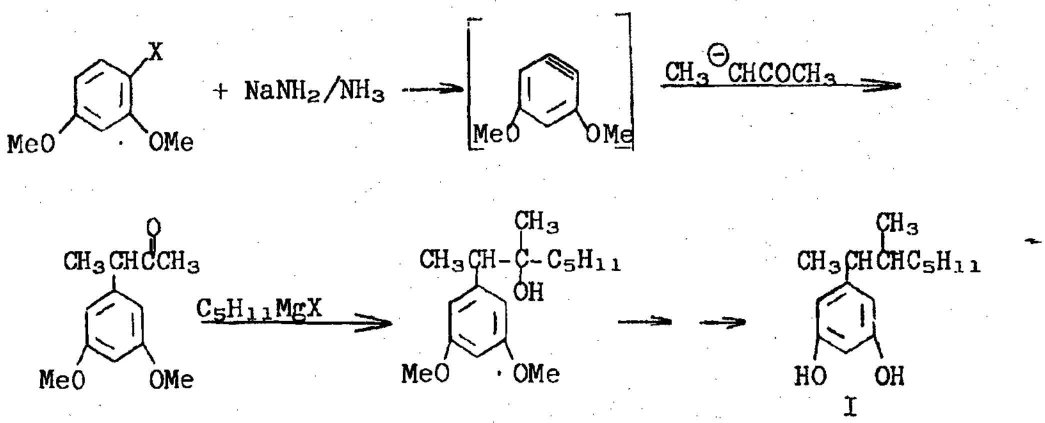
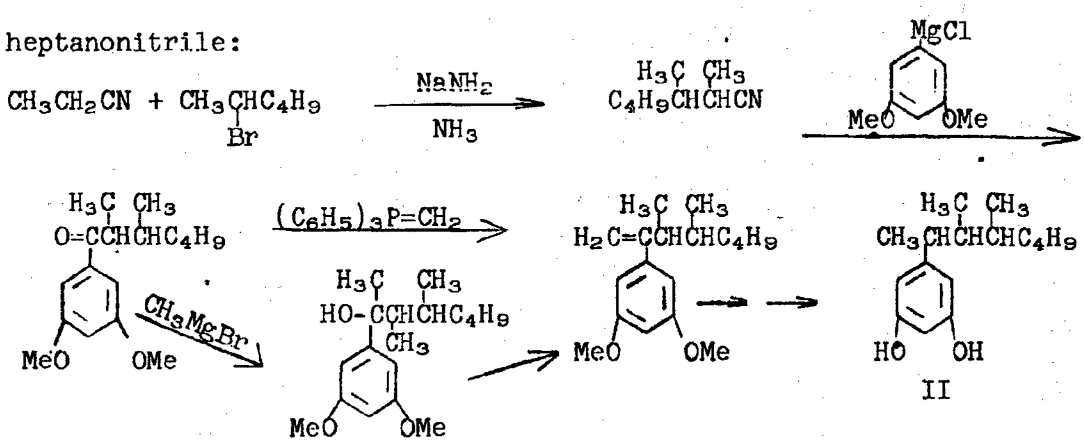
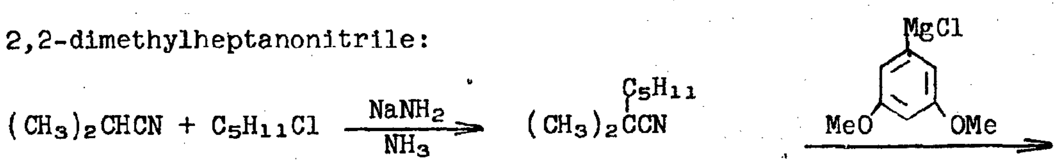
The route via direct resorcylation of butanone:

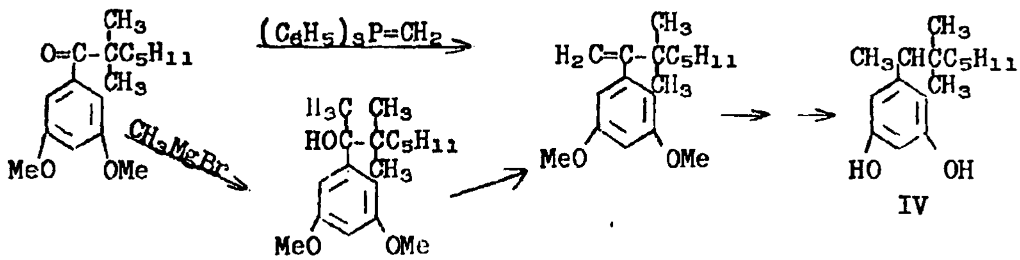


C. SYNTHESIS OF RESORCINOL II This route is based on the reaction of 3,5-dimethoxyphenylmagnesium chloride and 2,3-dimethylheptanonitrile:



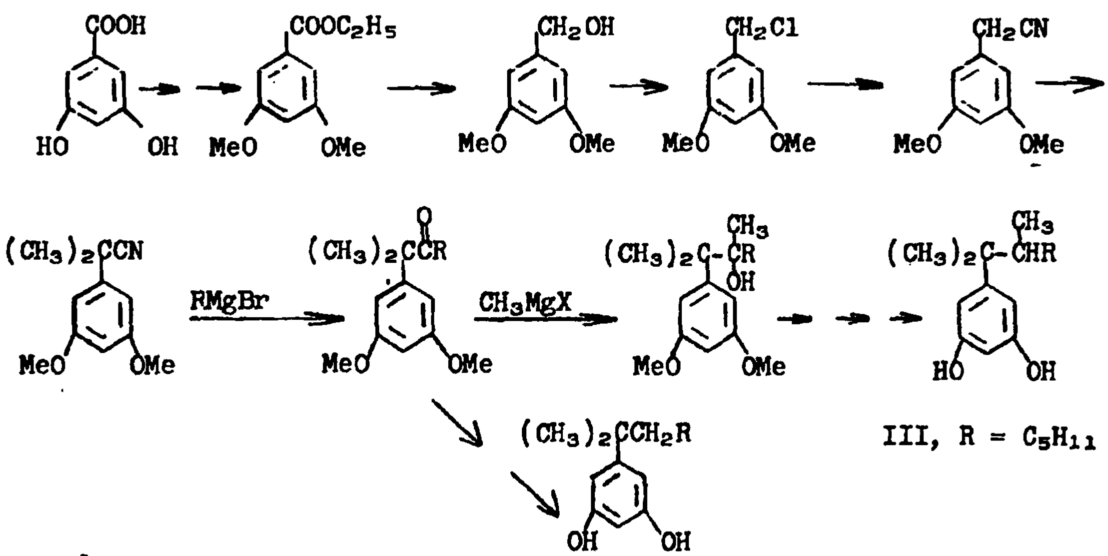
D. SYNTHESIS OF RESORCINOL IV Similarly to the above route, this one is based on the reaction of the same Grignard reagent with 2,2-dimethylheptanonitrile:





IV

E. ROUTES TO RESORCINOLS III, VI, and VII VIA 2-(3,5-DIMETHOXYPHENYL)-2-METHYLPROPIONITRILE This nitrile can be reacted with an alkyl Grignard reagent to form precursors of three of the desired resorcinols.



III, R = C_5H_{11}

VI, R = C_3H_7
VII, R = C_4H_9

These routes provide practical syntheses of III, VI, and VII. No convenient route for resorcinol V is presently available.

II. DISCUSSION OF RESULTS

A. GRIGNARD ROUTES TO 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE (I)

The recommended route to resorcinol I is from 1,3,5-trichlorobenzene by a Grignard route using 2-methylheptanonitrile. The details of this route make up much of this report and are summarized in section III. A.

The Grignard routes share six common intermediates: 1-chloro-3,5-dimethoxybenzene, the corresponding Grignard reagent, 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 and its dehydration, reduction, and cleavage products. They differ in the source of 1-chloro-3,5-dimethoxybenzene and in whether the Grignard reagent is reacted with 3-methyloctanone-2 or with 2-methylheptanonitrile.

1. 1-Chloro-3,5-dimethoxybenzene

Six routes to this intermediate were investigated, and a seventh was considered. They are presented in order of decreasing practicality.

a. From 1,3,5-Trichlorobenzene The reaction of 1,3,5-trichlorobenzene (1,3,5-TCB) with sodium methoxide in refluxing diglyme (the dimethyl ether of diethylene glycol) was investigated in detail, and the results are summarized in Table 1.

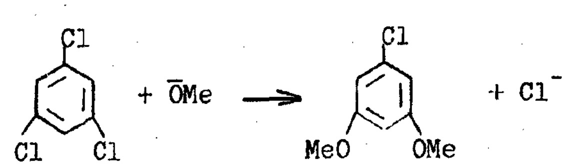
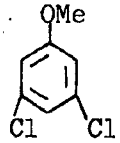


Table 1

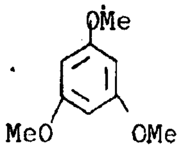
METHANOLYSIS OF 1,3,5-TCB

Run	Moles of 1,3,5-TCB	Moles of NaOMe	Mole Ratio	Volume of Diglyme ml	Time of Reflux hr	Yield of Product % Based on VPC
A	0.30	0.72	1:2.4	175	20	42
B	0.25	0.55	1:2.2	140	41	50.5
C	0.25	0.55	1:2.2	35	41	50
D	0.25	0.55	1:2.2	17.5	41	34
E	0.25	0.525	1:2.1	100	40.5	52
F	0.151	0.302	1:2.0	45	40.5	56
G	1.622	3.41	1:2.1	500	42	70

While the best results, on the basis of yield, were obtained at lower molar ratios of 1,3,5-TCB to sodium methoxide, the purity of the product was best, 95 area-% by vapor phase chromatography (VPC), at a molar ratio of 1:2.2. The by-products obtained are 3,5-dichloroanisole (VIII) from incomplete substitution, and 1,3,5-trimethoxybenzene (IX) from complete substitution.



VIII



IX

VIII has a boiling point fairly close to that of the desired product but may be removed by careful fractionation. IX is higher boiling and may be easily removed by simple distillation. Since a higher ratio of methoxide to 1,3,5-TCB would favor more complete substitution it is easy to see why the product obtained had a higher purity. Using a molar ratio of 1:2 the product was obtained in 89 area-% purity after simple distillation with the major impurity (10 area-%) being 3,5-dichloroanisole. The higher yield obtained in run G was probably due to the larger scale, which reduced mechanical losses to one-sixth of those in the other runs (on a percentage basis). It must be pointed out that in all of this work simple distillation set-ups were employed because yields could be determined by VPC rather than by isolation. On a large scale, efficient fractionation led to good yields of the desired product of 99 area-% purity.

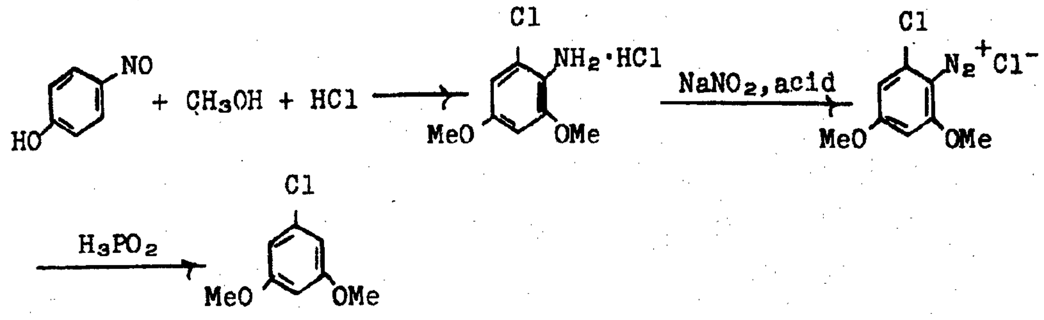
Table 1 also shows that the amount of solvent employed was gradually reduced from 585 ml per mole of 1,3,5-TCB in run A to 68 ml per mole of 1,3,5-TCB in run D. The latter concentration was too low, being insufficient for adequate mixing of the reactants. The minimum amount of solvent advisable appears to be about 1 mole (141 ml) per mole of 1,3,5-TCB. As the amount of solvent is decreased, the amount of by-product 3,5-dichloroanisole (VIII) formed increases to 29% in run D.

The much higher yield in run G, as compared to runs B, C, E, and F, reflects the relative decrease in mechanical losses because of the scale-up.

The desirability of this reaction as a route to 1-chloro-3,5-dimethoxybenzene over its preparation from p-nitrosophenol (Section II, A.1.b, below) depends on a favorable cost figure for 1,3,5 TCB. The Morton Chemical Company has indicated (12) a price of $0.75 to $1.00 per pound in large volume production.

Assuming a 68% yield of 1-chloro-3,5-dimethoxybenzene, $0.85/pound cost of 1,3,5-TCB, and 90% recovery of diglyme, the raw material cost per pound of 1-chloro-3,5-dimethoxybenzene from 1,3,5-TCB would be $1.88. This does not take into account the recycling of the by-product, 3,5-dichloroanisole, which could be treated with methoxide to yield more product. The raw material cost of the nitrosophenol route has been roughly estimated (see next page) at $3.46 per pound. Preparation of the chloride from 1,3,5-TCB is also much simpler from a mechanical point of view, which would make it much more attractive even without the marked reduction in raw material costs.

b. <u>From p-Nitrosophenol</u> This reaction sequence has been described by Goldschmidt and Suchanek(33).



p-Nitrosophenol was converted to 2-chloro-4,6-dimethoxyaniline hydrochloride by hydrogen chloride and methanol at room temperature. The amine hydrochloride was diazotized and deaminated to form 1-chloro-3,5-dimethoxybenzene. The scheme was carried out without isolation of the 2-chloro-4,6-dimethoxyaniline or its hydrochloride, in an overall yield of 37%.

The raw materials cost for one pound of product by this route is based on these required materials, assuming the 37% yield:

Reagent	Unit Cost	Quantity	Cost
p-nitrosophenol	\$ 1.05/lb	1.79 lb	\$ 1.88
CH_3OH	0.30/gal	1.03 gal	0.08‡
HCl (gas)	0.32/lb	2.06 lb	0.66
HCl (aq., conc.)	0.175/lb	4.24 lb	0.74
$NaNO_2$	0.10/lb	1.0 lb	0.10
			\$ 3.46

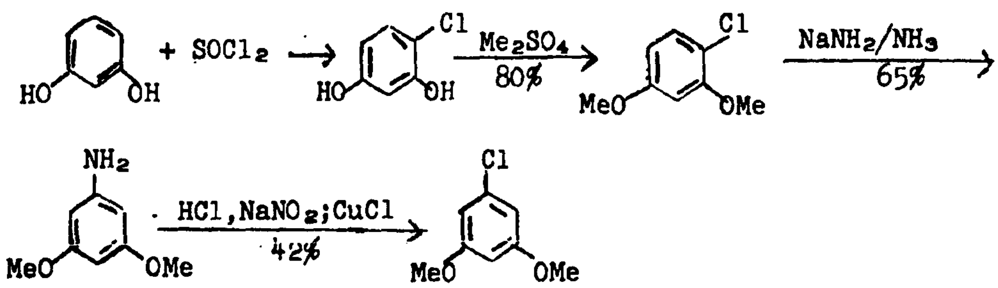
‡Assuming 75% recovery of methanol used.

Hypophosphorous acid was used for the deamination in the laboratory, but deamination on a production scale would undoubtedly be done by heating(33) or in the presence of a low cost alcohol such as isopropyl.

On a laboratory scale, this route requires only 3 man days.

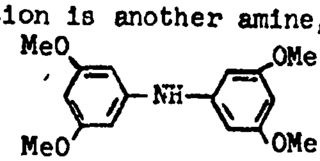
This route to 1-chloro-3,5-dimethoxybenzene is intermediate in cost and in labor between the methoxylation of TCB and the benzene route from resorcinol, below.

c. From Resorcinol (The Benzyne Route) This route to 1-chloro-3,5-dimethoxybenzene, which makes use of the benzyne reaction, has been referred to as the benzyne route in the first year's reports.



The first two steps could be carried out in either order, depending on the yield and convenience in handling. Experimentally, we started from the commercially-available 4-chlororesorcinol and investigated its methylation. The preparation of 4-chlororesorcinol has been described (19).

The diether of 4-chlororesorcinol was treated with sodamide in liquid ammonia to form 3,5-dimethoxyaniline via a benzyne intermediate.

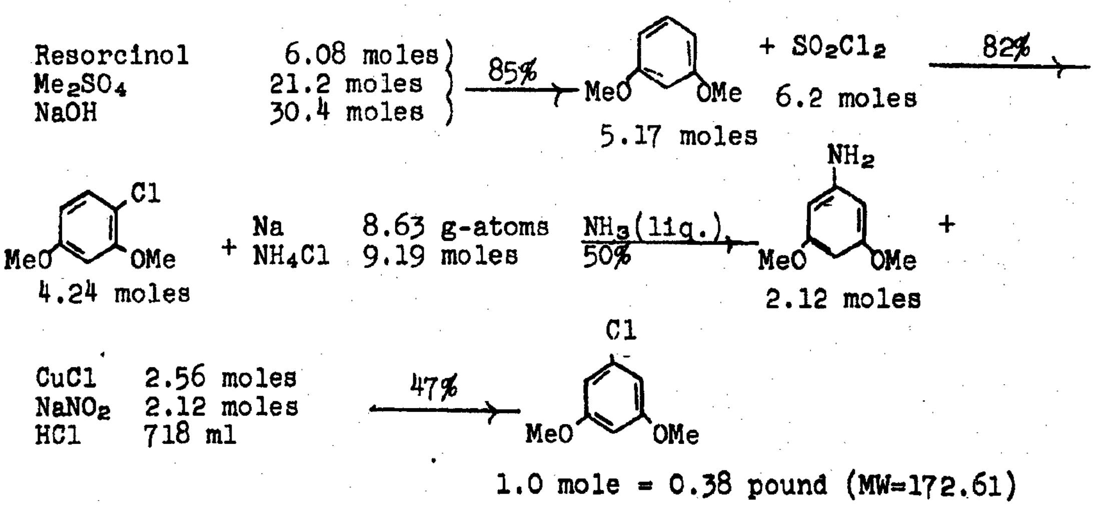
A by-product of the benzyne reaction is another amine, thought to be bis(3,5-dimethoxyphenyl)amine, 

, a new compound.

The aniline was subjected to the Sandmeyer reaction to produce the desired 1-chloro-3,5-dimethoxybenzene. The major limitation in this sequence is the Sandmeyer step, which proceeds in low yields and requires the use of an expensive reagent, cuprous chloride. It is possible that part of the cost of the cuprous chloride might be offset by recovery of the copper salts.

The best overall yield from 4-chlororesorcinol to 1-chloro-3,5-dimethoxybenzene obtained was 22%.

The raw materials cost for the preparation of 1-chloro-3,5-dimethoxybenzene from resorcinol is based on these requirements, per pound of product, using our best yields:



To prepare one pound, the following materials would be required:

Reagent	Cost† per pound	Wt, lb	Cost
NaOH	$ 0.05	7.05	$ 0.386
Me_2SO_4	0.175	17.34	2.711
Resorcinol	0.79	3.94	3.132
SO_2Cl_2	0.13	4.86	0.632
Na	0.20	1.16	0.232
NH_4Cl	0.10	2.84	0.284
CuCl	0.43	1.47	0.634
$NaNO_2$	0.10	0.84	0.084
HCl (aq. conc.)	0.175	3.95	0.684
			$ 8.873

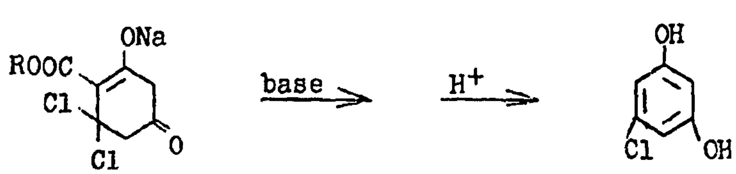
†Prices are all commercial prices and, in general, are the lowest possible.

The cost of liquid ammonia was not included since it should be largely recoverable. Cost of the cuprous chloride in materials plus labor should be increased slightly since it must be freshly prepared for the reaction, and the commercial material at $0.43 per pound will not work. However, against this there would be a cost reduction if any copper salts could be recovered from residues and recycled or sold.

On a laboratory scale, this route requires 7 man days.

d. 5-Chlororesorcinol from 4,4-Dichlorobuten-3-one-2 The contemplated reaction sequence was:

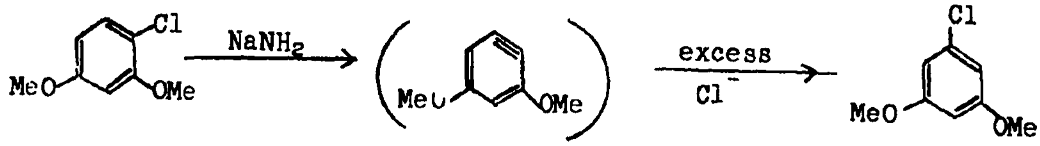
$$CH_3COCl + Cl_2C{=}CH_2 \xrightarrow{AlCl_3} [Cl_3CCH_2\overset{O}{\overset{\|}{C}}CH_3] \rightarrow Cl_2C{=}CH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{NaCH(COOR)_2}$$



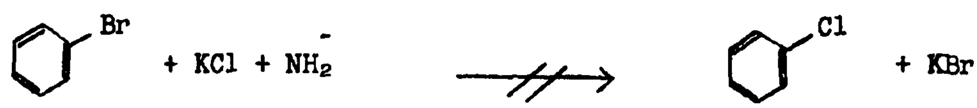
The first step was carried out using a modification of the literature procedure (38) and resulted in an 80% yield of 4,4-dichlorobuten-3-one-2. The second step was carried out using the sodium derivative of dimethyl malonate, and no definable product was obtained. However, a basic work-up procedure was employed, and, if dehydrohalogenation occurred before decarboxylation in the work-up of X, then the product obtained would probably be methyl 2-chloro-4,6-dihydroxybenzoate. From the latter, under basic conditions, several products might be obtained.

When this reaction sequence was proposed, it was felt that it could compete economically with the p-nitrosophenol route if it went in reasonable yield. Now, with the availability of the route to 1-chloro-3,5-dimethoxybenzene from 1,3,5-TCB described above, it appears that the subject reaction sequence could not compete even if the second step were quantitative.

e. Attempted Preparation from Lithium Chloride and Dimethylformamide on 1-Chloro-2,4-dimethoxybenzene This route was an attempt to improve the benzyne route from resorcinol by eliminating its most troublesome feature: the Sandmeyer reaction on 3,5-dimethoxyaniline. The benzyne route might still have been competitive if it were possible to convert 1-chloro-2,4-dimethoxybenzene to 1-chloro-3,5-dimethoxybenzene without the necessity of proceeding through the aniline derivative. This might be accomplished by dehydrohalogenation of 1-chloro-2,4-dimethoxybenzene, followed by reaction of the resultant benzyne intermediate with excess chloride ion.

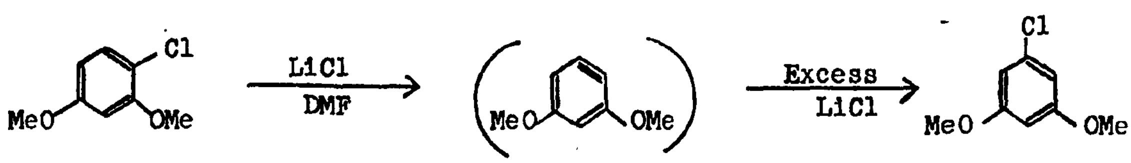


However, the literature reveals that a similar experiment was tried without success(97).



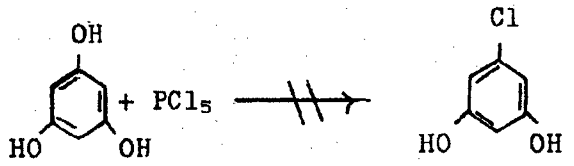
That experiment was unsuccessful even though bromobenzene is significantly more reactive toward alkali amide than is chlorobenzene.

The dehydrohalogenation of certain halo-ketones with lithium chloride in N,N-dimethylformamide has been investigated by R. P. Holysz(43). It was suggested(55) that we employ this method in an attempt to prepare 1-chloro-3,5-dimethoxybenzene.

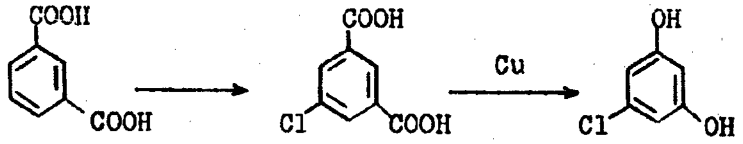


This method seemed quite speculative, since Holysz' work was done on haloketones; whereas, to be successful our experiment would involve the dehydrohalogenation of an aryl halide. However, a single experiment was carried out. Although intense color formation was observed, only starting material, 1-chloro-2,4-dimethoxybenzene, was recovered from the reaction mixture.

f. <u>Attempted Reaction of Phloroglucinol and Phosphorus Pentachloride</u> One unsuccessful attempt was made to prepare 5-chlororesorcinol directly by the chlorination of phloroglucinol with phosphorus pentachloride.

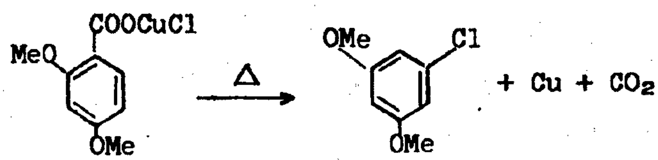


g. <u>From Aromatic Carboxylic Acids in the Presence of Copper</u> In view of the patent literature (49) pertaining to the conversion of aromatic carboxylic acids to phenols, isophthalic acid, which is relatively cheap (18¢/lb), was considered as a possible source of 5-chlororesorcinol.



However, a recent publication (88) by Toland regarding the mechanism of this reaction eliminated this idea from consideration for two reasons. First, the incoming hydroxyl group always occupies a position <u>ortho</u> to the carboxylic acid group it is replacing, and, second, phthalic acids do not yield dihydric phenols.

However, Toland pointed out that he could see no reason why other groups could not be introduced in the same manner. On this basis the following reaction might be worth considering.



This reaction would start with 2,4-dihydroxybenzoic acid, which is the most available of all the dihydroxybenzoic acids.

h. <u>From Resorcinol Dimethyl Ether</u> A long and unwieldy synthesis of 5-chlororesorcinol from resorcinol dimethyl ether (20) was not considered practical. It was not investigated.

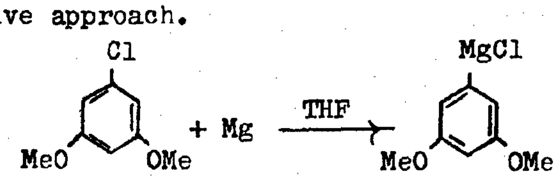
2. <u>3,5-Dimethoxyphenylmagnesium Chloride</u>

The difficulty in forming Grignard reagents from aryl chlorides is well known[27,28]. Chlorobenzene, the first member of the series, forms a Grignard reagent only when special conditions are used. Phenylmagnesium chloride has been prepared without a solvent at elevated temperatures[30] or in the presence of certain activators[31,69,94]

Methods of formation of Grignard reagents from other aryl chlorides have appeared in the literature. These compounds were prepared by using molar quantities of ethyl bromide[26] or ethylene bromide[64] as an entrainment carrier for the aryl chlorides. With ethylene bromide and magnesium, only ethylene and magnesium bromide are formed as by-products. Thus, only the Grignard reagent of the "inert chloride" is formed, and a mixture of two Grignard reagents, which would have resulted if ethyl bromide had been used, is avoided.

In 1954, Normant[61] reported the successful preparation of phenylmagnesium chloride and p-chlorophenylmagnesium chloride using tetrahydrofuran as solvent. Ramsden and coworkers[71] have recently elaborated on the work begun by Normant. These workers have reported that every aryl chloride tried reacted with magnesium in

tetrahydrofuran. Referring to this work, Pearson points out (64) that tetrahydrofuran is a more powerful coordinating solvent than diethyl ether. In the addition of the Grignard reagent complexed with tetrahydrofuran to slowly reacting carbonyl compounds, lower yields or even side reactions may take place. Ramsden has answered (70) this objection by devising methods of displacing tetrahydrofuran with higher boiling linear ethers after the formation of the Grignard reagent and prior to subsequent reaction of the Grignard reagent with carbonyl compounds. With the single reservation that the addition of the Grignard reagent might be retarded, the use of tetrahydrofuran (the "reactive solvent method") was an extremely attractive approach.

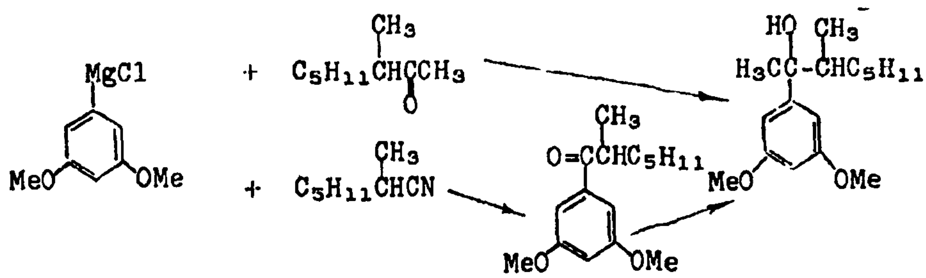


The solventless technique, the entrainment method, several of the activators which have been reported, and using magnesium powder plus ethylene bromide, (79) were all tried in unsuccessful attempts to make 3,5-dimethoxyphenylmagnesium chloride. Only the reactive solvent method in tetrahydrofuran proved successful. Following Ramsden's (71) procedure, the desired Grignard reagent was prepared in 79% yield.

An attempt to modify this method by using the mixed solvent system tetrahydrofuran-N-methylmorpholine, suggested by a consultant (89), resulted in no Grignard formation.

3. 2-(3,5-Dimethoxyphenyl)-3-methyloctanol-2

This intermediate can be obtained by reaction of the Grignard reagent above with 3-methyloctanone-2 or by a two-step reaction via 2-methylheptanonitrile.



a. Synthesis of 3-Methyloctanone-2 Six routes to this key intermediate were examined experimentally, and another was considered. Although we concluded that 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 could be prepared more practically via 2-methylheptanonitrile, this part of the investigation was extremely important, since this ketone had long been considered the key to the synthesis of the desired resorcinol.

The routes are arranged in order of practicality, as far as possible. The first three methods listed are far more practical then any of the others.

(1) 3-Methyloctanone-2 by Direct Alkylation of Butanone Butanone is alkylated directly with amyl halide, using sodamide in liquid ammonia as the condensation medium.

$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3 + NH_2^- \longrightarrow CH_3\overset{O^-}{\overset{\|}{C}}CHCH_3 + NH_3$$

$$C_5H_{11}X + CH_3\overset{O^-}{\overset{\|}{C}}CHCH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}\underset{C_5H_{11}}{\underset{|}{C}}HCH_3 + X^-$$

Using amyl bromide a 47% yield of 3-methyloctanone-2 was obtained. A preliminary experiment using a two-flask method had given only a 36% yield, evidently because the sodium salt of the enolate anion was too insoluble to be conveniently transported as a slurry from one flask to the other in the two-flask method.

The yield was further raised to 54% by using a greater amount of butanone and sodium: two moles of each to one mole of amyl bromide. The previous ratio was 6:5. Since the sodium and butanone make up a relatively small portion of the raw material cost of 3-methyloctanone-2 by this route, increasing their concentration does not increase the raw material cost if the yield of product increases enough to balance the added cost by reducing the amount of bromide required. The validity of this statement could be confirmed by a detailed development study of the amylation coupled with careful economic evaluation of every modification made.

Alkylations using amylating agents other than amyl bromide were not as successful. When amyl chloride was substituted for the bromide, no 3-methyloctanone-2 was obtained. In fact there seemed to be little or no ketol formation, a secondary reaction that was very much in evidence in the experiment using the bromide.

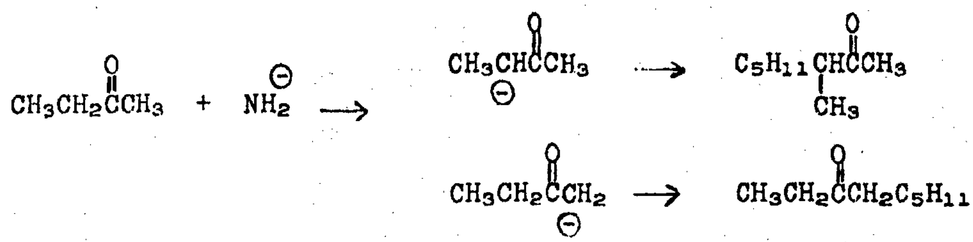
This negative result was unexpected. It was surprising that the use of the chloride should have had such a large effect on the yield. In order to demonstrate that the failure was not due to faulty experimental technique, two reactions were set up and carried out under identical conditions. In one case amyl chloride was employed and in the other amyl bromide was used. In spite of the great care exercised in keeping conditions identical, the run using the chloride failed to produce any ketone while that in which the bromide was employed resulted in a 47% yield (by VPC) of 3-methyloctanone-2.

The literature on the alkylation of ketones[91] shows clearly enough that the alkyl chlorides would be expected to react slower in this reaction than the bromides, but we were disappointed to find no product from the chloride in this case.

The alkylation with amyl chloride was repeated using 0.1 mole of sodium bromide per mole of amyl chloride, but no significant amount of 3-methyloctanone-2 was obtained. This particular technique had been suggested by the Chemical Corps. It had been found useful for alkylation of amines.

In another attempt to find an amylating agent cheaper and more effective than amyl bromide, the alkylation was carried out using diamyl sulfate, but the yield of 3-methyloctanone-2 obtained was only 28% by vapor phase chromatography (VPC).

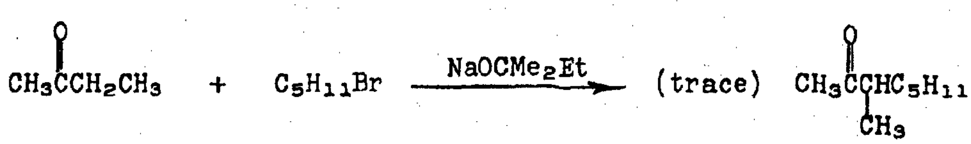
Each of the successful alkylations of butanone has also led to the formation of the isomeric ketone formed by reaction on the primary hydrogen: 3-nonanone.



The yield of 3-nonanone is 5-8%. This ketone is isomeric with the desired 3-methyloctanone-2 and cannot be separated from it by distillation, although separation via an appropriate carbonyl derivative might be feasible.

The best conditions found to date for the direct amylation of butanone are the use of two moles each of butanone and sodium per mole of amyl bromide. This gives 54% 3-methyloctanone-2 and 5.2% 3-nonanonc. Thus, the ketone that could be isolated would be an isomeric mixture containing only 91% 3-methyloctanone-2.

The preparation was attempted again using sodium t-amyloxide as the base in place of saodamide. The followed work of Conia [22].



The alkylation with sodium t-amyloxide was attempted in toluene and in ether. The use of ether was recommended where the ketone is especially prone toward self-condensation, since the enolate ion is supposedly more stable in ether than in toluene[22]. 3-Methyloctanone-2 was formed in only trace amounts (1-2% yields based on VPC) together

with lesser quantities of the usual contaminant, 3-nonanone (0.3-0.4% yields based on VPC). Both experiments led to the recovery of about one-third unaltered alkylating agent, amyl bromide. The major products were α,β-unsaturated ketones, a pair lower boiling and a pair higher boiling than the desired ketone. These ketones could result by dehydration of the di- and tri- self-condensation products of butanone

Conia's work (22) raises the hope that a more careful choice of alkylating agent and ketone might lead to more favorable results. He observed that dimethyl sulfate was the most reactive alkylating agent in the sodium t-amyloxide-toluene (or ether) base-solvent system. One could attempt the alkylation of octanone-2, a ketone less susceptible toward self-condensation than butanone, with dimethyl sulfate.

The final evaluation of the merits of the direct alkylation route to 3-methyloctanone-2 should also consider whether or not a separation of the isomers is feasible and what the effect on the efficacy of the ultimate agent would be if it were derived from a mixture of these isomers. It might also develop that the rate of reaction of the two ketones with 3,5-dimethoxyphenylmagnesium chloride is sufficiently different to enrich the product carbinol with the desired side-chain.

(2) 3-Methyloctanone-2 from 2-Methylheptanonitrile

3-Methyloctanone-2 can also be prepared by the alkylation of propionitrile to 2-methylheptanonitrile, followed by the reaction of the latter with methyl Grignard to form the desired ketone.

$$CH_3CH_2CN + C_5H_{11}X \xrightarrow{Na/liq.\ NH_3} C_5H_{11}\overset{CH_3}{\overset{|}{C}}HCN \xrightarrow[Et_2O]{CH_3MgBr} C_5H_{11}\overset{CH_3}{\overset{|}{C}}H\underset{O}{\underset{\|}{C}}CH_3$$

Propionitrile was alkylated[98] with 1-chloropentane using sodium in liquid ammonia to give a 64% yield of 2-methylheptanonitrile. Some higher-boiling by-product, presumed to be 2-amyl-2-methylheptanonitrile, was also obtained.

The 2-methylheptanonitrile was reacted with methylmagnesium bromide. After hydrolysis, distillation resulted in the isolation of a 76% yield of 3-methyloctanone-2 in 91 area-% purity. The major contaminant, 8 area-%, was unreacted 2-methylheptanonitrile, which could not be conveniently separated by distillation. Increasing the amount of Grignard reagent up to a 25% excess did not result in any improvement.

One unsuccessful attempt was made to hydrolyze the unreacted nitrile so that the acid and ketone could then be separated by either distillation or extraction with dilute base. More work could be done to improve this route to the ketone if the other problems associated with the route via 3-methyloctanone-2 are resolved.

(3) By the Alkylation of Acetoacetic Ester Ethyl 2-acetylpropionate, a monoalkylated ethyl acetoacetate, was purchased and alkylated[72] with iodopentane and potassium in *t*-amyl alcohol to ethyl 2-acetyl-2-methylheptanoate of 95 area-% purity by VPC, and 76% yield.

$$CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{CH}COOEt + C_5H_{11}I \xrightarrow{KOCMe_2Et} CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_3}{\overset{C_5H_{11}}{C}}COOEt$$

The same ester had also been obtained by the alkylation in the reverse order (amylation followed by methylation), but in that case, the boiling point of the ethyl 2-acetylheptanoate was too close to that of the dialkylated ester for convenient separation. The yield, based on VPC (but not isolable), was 79% of 92 area-% purity. Substitution of sodium in _t_-amyl alcohol for the potassium lowered the yield to 36%, but the yield was unaffected by the use of commercial potassium _t_-butoxide.

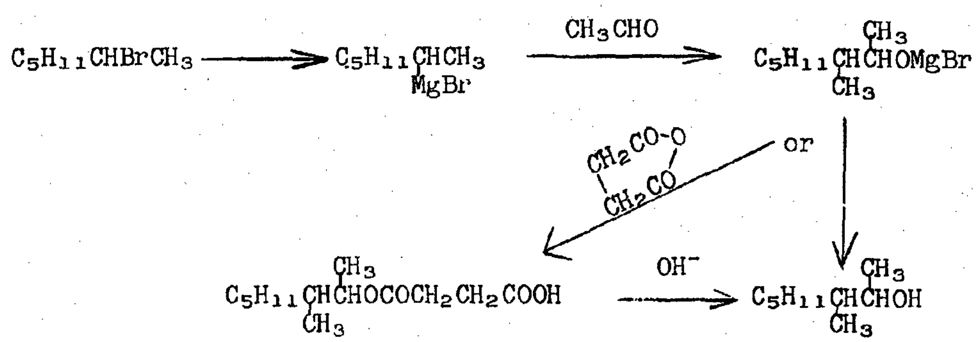
Ethyl 2-acetyl-2-methylheptanoate was converted to 3-methyloctanone-2 by decarboxylation using potassium hydroxide in refluxing aqueous methanol[72].

$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_3}{\overset{C_5H_{11}}{C}}COOEt + OH^- \xrightarrow{-CO_2} CH_3\overset{O}{\overset{\|}{C}}CHC_5H_{11}$$

3-Methyloctanone-2 of 98 area-% purity was obtained in 64% yield. The overall yield of 3-methyloctanone-2 from ethyl acetoacetate by this method is 36%.

Although this route could not be commercially practical on a large scale, because of the low overall yield and relatively high cost it is useful for laboratory preparations since the ketone prepared is not contaminated with nitrile or with any close-boiling adulterant.

(4) From Acetaldehyde and 2-Heptylmagnesium Bromide 2-Heptylmagnesium bromide was reacted with acetaldehyde to form 3-methyloctanol-2, which was then oxidized to the desired ketone. One preparation of this alcohol proceeded through the succinic acid half-ester; the second avoided the use of this intermediate.

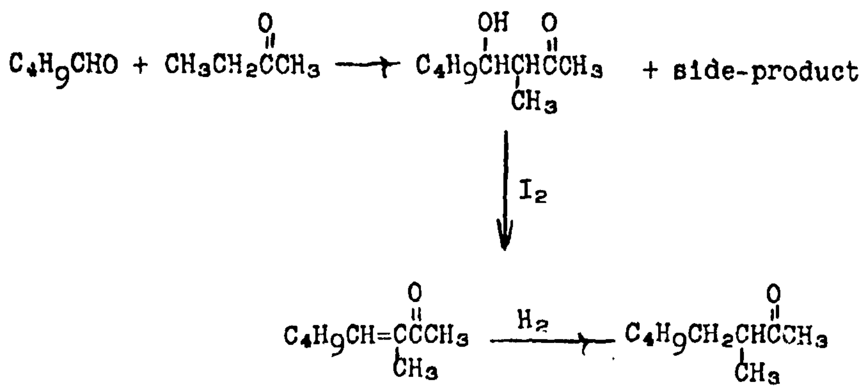


The use of the succinic acid half-ester followed a literature procedure[1] and resulted in a 57% yield of 3-methyloctanol-2 94% pure by VPC. This alcohol was oxidized with dichromate according to Powell's procedure[65] to give a 65% yield of 3-methyloctanone-2.

When the unusual use of succinic anhydride was eliminated from the procedure, a mixture of 27% 3-methyloctanol-2 and 13% 3-methyloctanone-2 was formed, which could be oxidized to the pure ketone in 73% yield. This method, although resulting in lower total yield, requires about half the work of the succinic acid half-ester method when done on the laboratory scale.

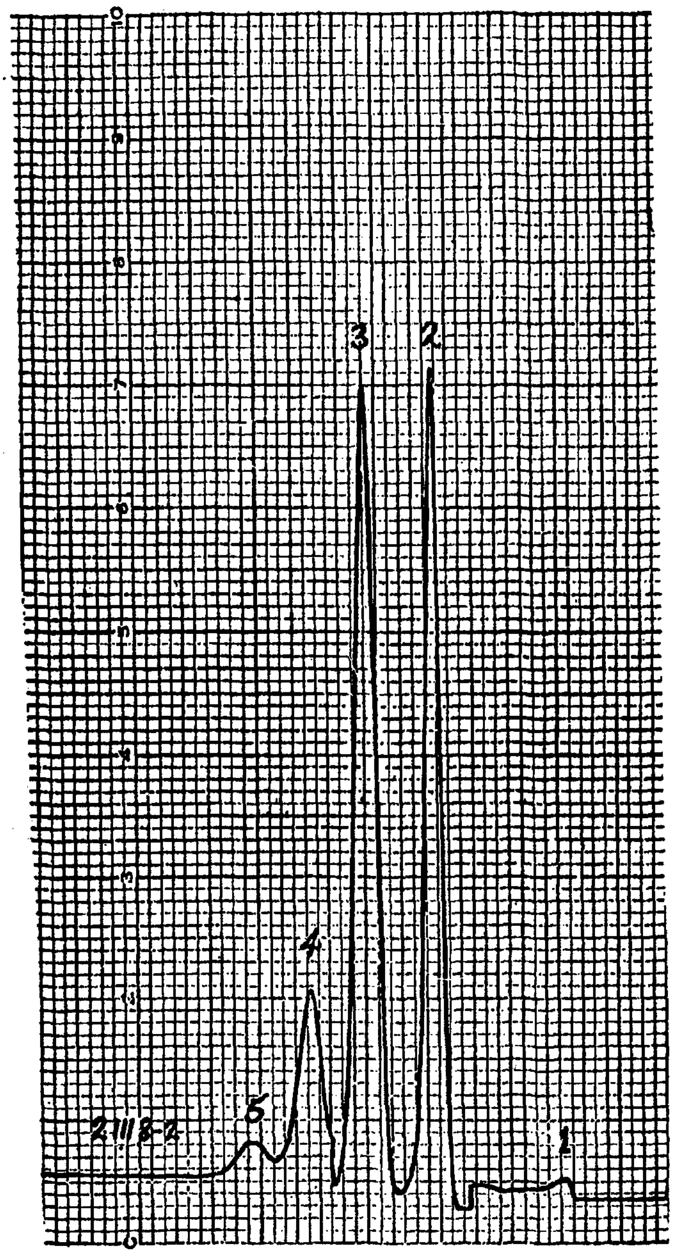
Whether or not the succinic acid half-ester is made, the preparation of 3-methyloctanone-2 by the Grignard reaction with acetaldehyde is impractical because of mediocre yields and high cost.

(5) <u>From the Aldol Condensation of Butanone and Valeraldehyde</u> An approach to the synthesis of 3-methyloctanone-2 that has been used by another Chemical Corps contractor(87) is by the condensation of butanone and <u>n</u>-valeraldehyde(65,66), followed by dehydration and hydrogenation of the condensation product.



Interpretation of instrumental data on the supposed condensation and dehydration products, 4-hydroxy-3-methyloctanone-2 and 3-methyl-octene-3-one-2, was inconclusive, so the dehydrated material was hydrogenated.

The product of this hydrogenation was a mixture of two saturated ketones. The desired 3-methyloctanone-2 made up about 40 area-%, and an unknown ketone of higher retention time made up the other 60 area-% on the VPC of one distillation cut of this mixture, shown in Figure 1.



Component No.	Retention Time, min.	Area-%	Identification
1	1.9	0.6	
2	4.1	41.8	3-methyl-2-octanone
3	5.2	49.3	unk. sat'd ketone
4	6.2	6.9	
5	7.1	1.4	

Figure 1. Vapor phase chromatogram of sample 21118-2, lower-boiling fraction from reduced, dehydrated aldol of butanone and valeraldehyde; Perkin-Elmer Model 1540 Vapor Fractometer, 6' 16% m-bis-(m-phenoxyphenoxy)benzene on 35-80 mesh Chromosorb W, 151°, 85 cc He/min. Components 2 and 3 at twice the attenuation of the others.

The unknown saturated ketone was separated by VPC from one of the distillation cuts of the mixture in 98 area-% purity. The infrared spectrum of this component is shown in Figure 2. This component has a carbonyl absorption at 1712 cm^{-1} attributed to a saturated ketone (saturated aldehydes are expected at around 1730 cm^{-1} and saturated ketones at around 1715 cm^{-1})[15]. Further evidence that the unknown component was probably not an aldehyde was obtained from an infrared spectrum of the VPC-separated unknown component run at higher thickness. This spectrum showed no evidence of C-H stretching at about 2720 cm^{-1}, which would be characteristic of an aldehyde. This would seem to rule out the possibility that the unknown major component was 2-amylvaleraldehyde, arising from the self-condensation of valeraldehyde.

An isomeric ketone, nonanone-3, would arise if the original aldol reaction took place, in part, on the methyl carbon of the butanone instead of on the methylene carbon.

$$C_4H_9CHO + CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{?} CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2\underset{OH}{\underset{|}{C}}HC_4H_9 \longrightarrow \longrightarrow C_2H_5\overset{O}{\overset{\|}{C}}C_6H_{13}$$

In any event, the reaction scheme seems unsuitable as a source of the desired ketone. The conditions used were identical to those in the literature[65,66] and to those that were used by another Chemical Corps contractor[87] to make 3-methyl-2-octanol.

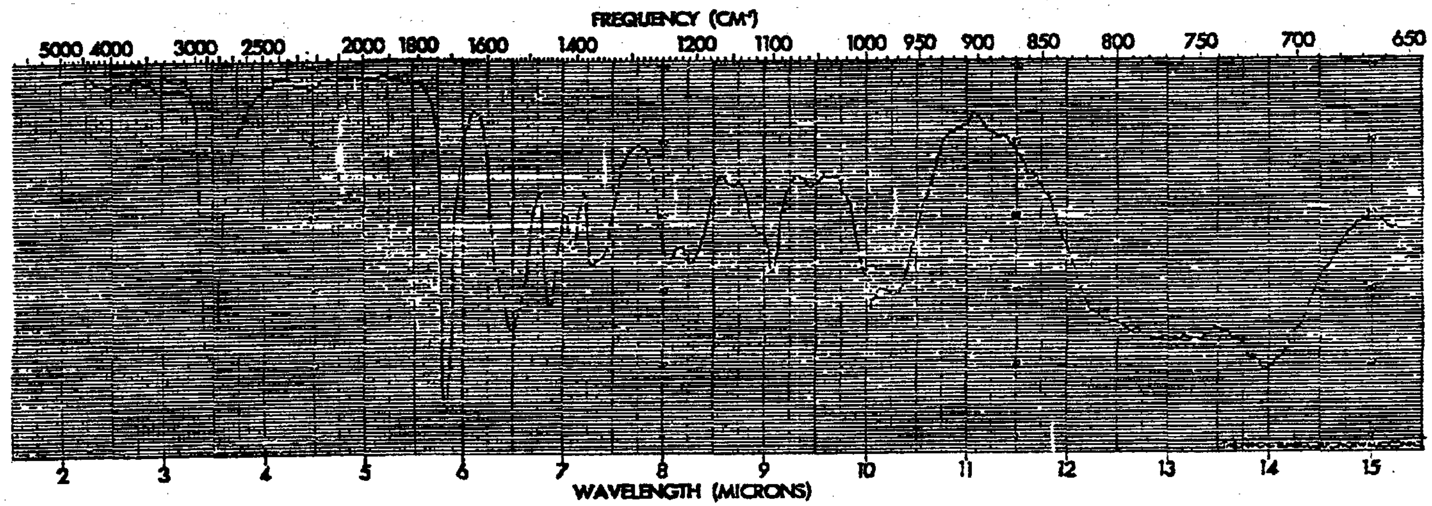
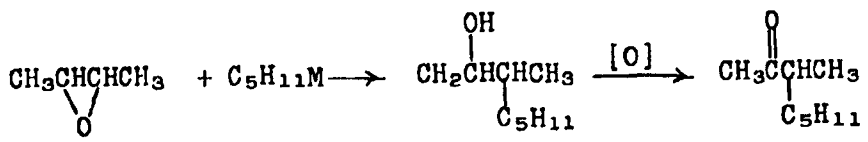


Figure 2. Infrared spectrum of 5.2 minute component of sample 21118-3, unknown saturated ketone from reduced, dehydrated aldol of butanone and valeraldehyde; Perkin-Elmer Model 21 double beam spectrophotometer, CCl_4 solution, sodium chloride optics. Sample 98 area-% pure by VPC.

(6) From Epoxybutane The reaction of 2,3-epoxybutane with an amyl organometallic was suggested in the hope that it would provide an unambiguous and relatively inexpensive route to the desired ketone.



(M = metal)

Reactions of this type have been reported(24), but the alkyl metall-organics give considerably lower yields than the aromatic analogs(77). The scheme had the advantage that only a single isomeric alcohol could be formed since the epoxide is symmetrical.

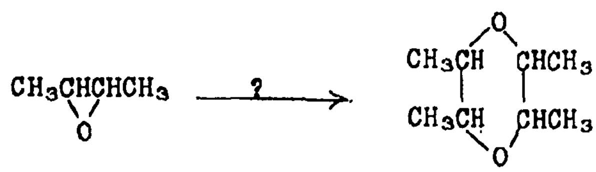
The use of amyl Grignard for $C_5H_{11}M$ was considered but rejected, since the presence of magnesium halide, a Lewis acid, in the Grignard reagent is known to catalyze the isomerization of epoxides to ketones (95).

Two experiments were performed using amyl sodium and 2,3-epoxybutane. The first experiment, utilizing commercial amyl sodium and 2,3-epoxybutane (1:1 molar ratio), resulted in a 2% yield (determined by VPC) of what apparently was the desired carbinol. The second experiment, utilizing 2,3-epoxybutane and amyl sodium <u>in situ</u> (2:1 molar ratio), resulted in a 6% yield of carbinol as determined by VPC.

A single experiment was performed using butyl lithium and 2,3-epoxybutane to see whether or not a lithium alkyl would react more favorably with 2,3-epoxybutane than had amyl sodium. Butyl lithium was chosen since it was readily available and behavior of this reagent should reflect potential behavior of amyl lithium. Butyl lithium was reacted with 2,3-epoxybutane (1:1 molar ratio), and resulted in only 6% yield of carbinol as determined by VPC.

The experiment with butyl lithium was carefully evaluated in an attempt to determine what had happened to the bulk of the starting epoxide. The carbinol produced by the reaction was most probably the desired one, since its infrared spectrum exhibited absorption characteristic of a secondary alcohol, bonded -OH at 3350 cm^{-1}, and C-O bend at 1100 cm^{-1}. A small quantity of material was obtained that exhibited infrared absorption characteristic of carbonyl function and ethylenic unsaturation. This suggests that a portion of the starting epoxide may have been isomerized to butanone, which then self-condensed to a ketol that underwent dehydration during distillation of the reaction products. Also a small amount of relatively high boiling hydrocarbon was detected, possibly a dimer of 3-methylheptene-2. Such a product could result by alfin catalysis[23] involving butyl lithium and lithium alkoxide on a reaction intermediate. The products previously discussed still do not account for the bulk of the starting epoxide. It would appear that most of the epoxide had been lost during the distillation of reaction solvents (hexane and octane) at atmospheric pressure. The infrared spectrum of re-

covered reaction solvent exhibited a medium intensity band at 1125 cm^{-1} that could be due to the presence of an alkyl ether. This absorption band was not exhibited by the starting epoxide. Such a product could be accounted for by the dimerization of the starting epoxide to sym-tetramethyldioxane. The dimerization of ethylene and propylene oxides to dioxanes is a known reaction(48).



Since the reaction of 2,3-epoxybutane with metal alkyls produced only negligible yields of carbinols, no major effort was made to prove the above conjecture. Sufficient evidence was obtained, however, to illustrate the complexity of this reaction, and its impracticality as a route to 3-methyloctanone-2.

Diethylmagnesium, free of magnesium halide, has been reported (96) to give a higher yield of 3-methylpentanol-2 with cis-2,3-epoxybutane than it does with the trans-isomer. This would suggest that the exclusive use of cis-2,3-epoxybutane would be required for optimum yields in the present experiment. Since only traces of the desired carbinol were obtained using the commerical mixture, which contains substantial proportions of both cis and trans-isomers, the results did not justify further investigation using pure cis-isomer.

(7) From the Oxo Reaction In the past there has been discussion of a preparation of 3-methyloctanone-2 via an aldehyde, 2-methylheptaldehyde, obtained from the oxo reaction. The over-all scheme would be:

$$C_5H_{11}CH{=}CH_2 \xrightarrow{\text{oxo}} C_5H_{11}\overset{CH_3}{\overset{|}{C}}HCHO$$

$$\xrightarrow{CH_3MgX} C_5H_{11}\overset{H_3C}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}HCH_3 \xrightarrow{[O]} C_5H_{11}\overset{H_3C}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}CH_3$$

The route has not been examined on a laboratory scale. Its cost is discussed below.

(8) Relative Costs of the Most Practical Routes to 3-Methyloctanone-2 A rough raw material cost calculation was made for the preparation of the ketone by the alkylation of butanone, assuming a 55% yield of 3-methyloctanone-2 from 1-bromopentane, the cost of liquid ammonia negligible since it should be recoverable, and 1-bromopentane available at $1.15/lb.

Raw Material	Cost/lb	Pounds required	Total cost
Butanone	$0.125	0.93	$0.116
1-Bromopentane	1.15	1.95	2.24
Sodium	0.16	0.318	0.045
Total raw material cost/lb of ketone			$2.301

The highest single raw material cost (97% of the total) is that of 1-bromopentane. It would be desirable to obtain a firm price quotation on this material in the required quantities. This is a one-step route.

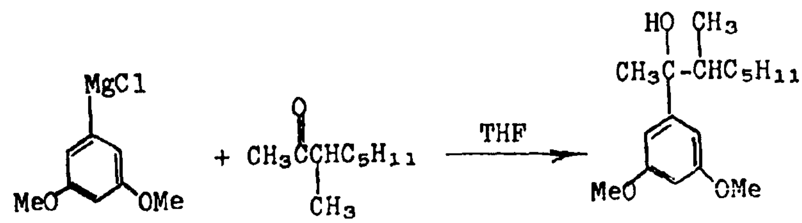
The preparation of 3-methyloctanone-2 via 2-methylheptanonitrile is based on propionitrile which, while not at present available in bulk, should easily be obtained at reasonable price by hydrogenation over palladium of acrylonitrile at 25 cents per lb or by the reaction of diethyl sulfate at 19 cents per lb with sodium cyanide at 19 cents per lb. The use of sodium in liquid ammonia for the alkylation would be both economical and easily handled on a large scale. This route has been successful with 1-chloropentane, the lowest priced of the amyl halides. The overall yield for the two-step route is 42%, corrected for purity.

The ethyl acetoacetate route has consistently given ketone of high purity (over 98 area-%) while the best material obtainable from propionitrile has been about 91% pure. The former route starts from ethyl acetoacetate at 58 cents per lb and involves two alkylations with potassium in t-amyl alchol, which would be an expensive condensation agent. In order to obtain the yield mentioned above, the alkyl iodides were used. Alkyl iodides are expensive and not readily available. To approach an economical process, the iodine would have to be recovered as potassium iodide. This would require additional processing. While substitution of the iodides by chlorides would greatly reduce costs, their use might appreciably lower the yield. The use of bromides would be expected to lower the yield somewhat and would also probably require recovery of the bromine as potassium bromide to be economical. The overall yield for the three-step route from ethyl acetoacetate is 36%.

In past discussions of the oxo reaction route, it was taken for granted that the oxo aldehyde would be inexpensive by analogy with common commercial examples. This line of reasoning is correct only if heptene-1 is available at a very low cost. Humphrey-Wilkinson Co. of North Haven, Conn., quoted a price to us of $2.25 per pound in 16,500 pound lots for heptene-1. While it is acknowledged that this price is unrealistic, it still might indicate that a good grade of the olefin would be fairly expensive. Since heptene-1 has an odd number of carbon atoms it is not likely to be available from the dimerization of propylene or some similar reaction. This, plus the fact that the oxo reaction would give two products, $C_5H_{11}\underset{}{\overset{CH_3}{CH}}CHO$ and $C_5H_{11}CH_2CH_2CHO$, could make 2-methylheptaldehyde fairly expensive.

Once this aldehyde is obtained, two more steps are required to get 3-methyloctanone-2. The first of these is a Grignard reaction, which should go in good yield. Grignard reactions are expensive, and, while they can be run on a large scale, they present some problems that are avoided by the more direct amylation of butanone. The other reaction required, the oxidation of 3-methyloctanol-2, should present no problems.

b. Reaction of 3-Methyloctanone-2 and 3,5-Dimethoxyphenylmagnesium Chloride This reaction proceeds to form the desired 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2, but its complication by a side reaction was not discovered until a large, preparative run was made.



The results of the distillation of a 0.67 mole run are shown in Table 2.

Table 2

DISTILLATION OF GRIGNARD REACTION PRODUCTS

	Cut 1	Cut 2	Cut 3	Cut 4
Boiling point, °C/mm	to 80/ 0.35	80-138/ 0.45	134-6/ 0.25	140-7/ 0.25
Weight, g	26.4	10.3	30.6	82.0
Products, area-%				
3-Methyloctanone-2	5.8	9.1	25.6	3.9
1-Chloro-3,5-dimethoxybenzene	16.5	46.0		
m-Dimethoxybenzene,	76.9			
unknown	1.0	23.0	39.2	3.6
2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 (desired product)		8.5	30.4	92.5

m-Dimethoxybenzene, which was the major component in the first fraction, was collected by VPC and identified by its infrared spectrum. This product could only arise from the hydrolysis of unreacted Grignard reagent. The amount obtained represents about 23% of the chloride used. In addition, 8% of the starting chloride was recovered unchanged. The following conclusions were reached as a result of these figures. First, Grignard formation could have occurred in as high as

92% of theory since only 8% of the starting chloride was recovered unchanged. Second, only 69% of the chloride used ever was involved in the formation of the desired product. This means that while the conversion to product was only 50%, the yield was 73%. Third, since a large amount of m-dimethoxybenzene (equivalent to 23% of the starting chloride) was recovered apparently owing to Grignard hydrolysis, a side reaction was competing with the Grignard reagent for the ketone.

A disturbing feature of the analytical results was the presence of the very low boiling starting ketone in all the distillation fractions regardless of boiling point. It would seem unlikely that this was original unreacted ketone but rather that it was forming as a result of a decomposition either during distillation or on the VPC column.

The unknown component was collected by VPC and its infrared spectrum obtained. It was not aromatic and its spectrum showed two carbonyl abosrptions and aliphatic unsaturation. It was concluded that this unknown is very likely an aldol condensation product of 3-methyloctanone-2 that undergoes thermal decomposition to the starting ketone on distillation.

The most reasonable explanation for all of the above observations is that the Grignard reagent is greatly deactivated by the very powerful coordination effect of the tetrahydrofuran solvent and therefore reacts slowly with the ketone. The Grignard intermediate ROMgCl is known to catalyze aldol condensations[35]. The following quotation is from a paper[41] by Hickinbottom and Schlüchterer. "The structure of the ketone is also an important factor (in condensation); those with an available hydrogen adjacent to the carbonyl and a slow rate of

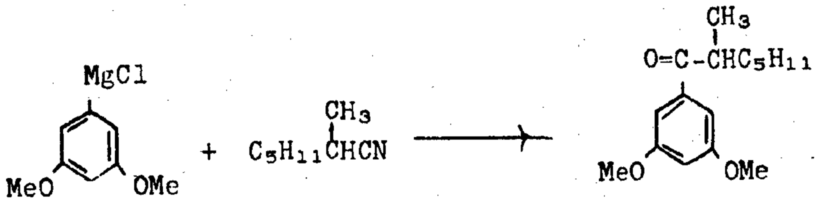
reaction toward Grignard reagents condense more readily. If they react with Grignard reagents which do not cause reduction, such as the arylmagnesium halides, the formation of the condensation is still more favored". Thus conditions are ideal for condensation, and in this particular case it competes very well with Grignard addition.

It was hoped that displacement of the tetrahydrofuran with a higher boiling solvent of weaker coordinating ability, such as dibutyl ether, or diglyme would increase the reactivity of the Grignard reagent to a point where condensation could not compete. Unfortunately, substitution of either of these solvents resulted in no decrease of the aldol side-reaction.

The side-reaction is perhaps the largest stumbling block in the way of the use of 3-methyloctanone-2. When 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 is formed from the Grignard reagent and 2-methylheptanonitrile and a subsequent Grignard step, no such aldol side-reaction is possible.

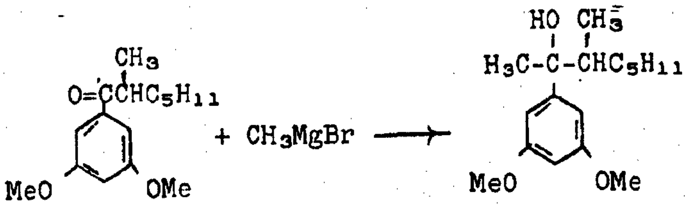
c. Reaction of 2-Methylheptanonitrile and 3,5-Dimethoxyphenylmagnesium Chloride: Synthesis of 2-(3,5-Dimethoxybenzoyl)heptane The preparation of 2-methylheptanonitrile from propionitrile was described above in Section II.A.3.a.2.

The reaction of 2-methylheptanonitrile with 3,5-dimethoxyphenylmagnesium chloride resulted in a 71% yield of 2-(3,5-dimethoxybenzoyl)heptane, 94 area-% pure by vapor phase chromatography (VPC).



The literature[36] indicates that similar reactions of aryl Grignard reagents with higher aliphatic nitriles have resulted in the isolation of aryl alkyl ketones in 80 to 90% yields. The probable reason for the lower yield in this case is incomplete Grignard formation. Indications are that the reaction of 1-chloro-3,5-dimethoxybenzene with magnesium has been producing Grignard reagent in only 70 to 80% of the theoretical yield. Taking this into consideration, the yield of 2-(3,5-dimethoxybenzoyl)heptane would be about 85%.

d. <u>2-(3,5-Dimethoxyphenyl)-3-methyloctanol-2 from 2-(3,5-Dimethoxybenzoyl)heptane (the Nitrile Route)</u> The reaction of 2-(3,5-dimethoxybenzoyl)heptane with methylmagnesium bromide resulted in a 93.5% yield of 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 based on VPC analysis of the cruct product. Distillation resulted in the isolation of this product in greater than 96 area-% purity.

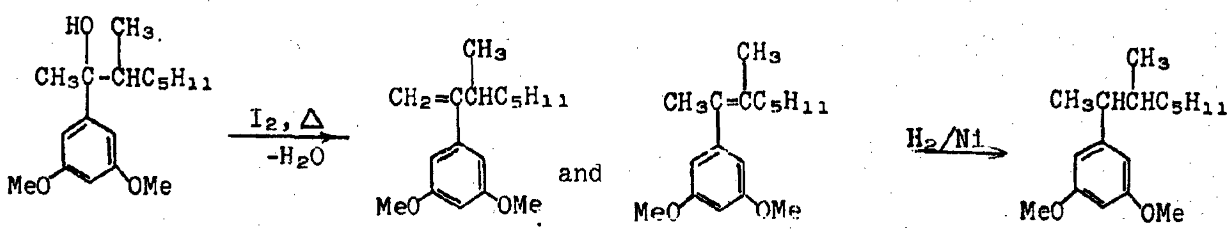


It must be noted that the nitrile route to 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 is the same as the ketone route when the ketone is prepared from 2-methylheptanonitrile. The only difference is the order in which 3,5-dimethoxyphenylmagnesium chloride, 2-methylheptanonitrile, and methylmagnesium bromide are reacted with one another. The over-all yield of 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 via 3-methyloctanone-2 prepared from 2-methylheptanonitrile and methylmagnesium bromide is 45%, while it is 62% when 2-methylheptanonitrile is first reacted with 3,5-dimethoxyphenylmagnesium chloride and the resulting 2-(3,5-dimethoxybenzoyl)heptane then reacted with the methylmagnesium bromide.

e. <u>Comparison of the Two Routes to 2-(3,5-Dimethoxyphenyl)-3-methyloctanol-2</u> The recommended route to this carbinol from 3,5-dimethoxyphenylmagnesium chloride is the route via 2-methylheptanonitrile.

The route via 3-methyloctanone-2 would be preferred if the self-condensation of that ketone during the Grignard reaction could be suppressed and if a really satisfactory and economical preparation of 3-methyloctanone-2 could be devised. After a reasonable effort we were unable to avoid the self-condensation and can see no solution to that problem. Evaluation of the projected preparation of 3-methyloctanone-2 from 2-methylhexaldehyde prepared by an oxo reaction would have to be made on the basis of cost information and estimation. Laboratory work might not be very helpful on that question. It appears quite certain from our work during the first year that 3-methyloctanone-2 can never be obtained by the aldol reaction of valeraldehyde and butanone unless a method for separating close-boiling isomeric products can be discovered, which is improbable.

4. <u>2-(3,5-Dimethoxyphenyl)-3-methyloctenes and 2-(3,5-Dimethoxyphenyl)-3-methyloctane</u> The dehydration of 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2 resulted in an 85% yield of 2-(3,5-dimethoxyphenyl)-3-methyloctenes-1 and -2 which was 95 area-% pure. According to the infrared spectrum, the mixture was predominantly the terminal olefin <u>dl</u> pair. The olefin mixture was reduced to the corresponding octane using 10% of 65% nickel-on-kieselguhr at 125°C and hydrogen at 1750-2500 psig for six hours.

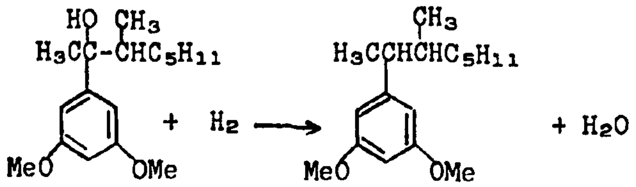


It was not possible to distinguish between the product and the olefin mixture using VPC and infrared, but the literature(1) indicates that ultraviolet will distinguish between these materials. The example in the literature involved 2-(3,5-dimethoxyphenyl)-3-methylheptene-2 and the corresponding heptane.

They found that the saturated material showed a minimum in the ultraviolet at 240-250 mμ while the olefin did not. Our product showed adsorption maxima at 272 and 278 mμ and a minimum at 247 mμ. The starting material did not show a minimum.

We frequently experienced difficulty with catalytic reductions of intermediates in this series, as have other workers(1). We were also unable to catalytically hydrogenolyze the carbinol, a substituted benzyl alcohol(8) using nickel-on-kieselguhr, copper chromite, or platinum oxide catalysts, pressures ranging from 50 to 2500 psig, and temperatures ranging from 30 to 250°C. These difficulties appear to be due to initial poisoning of the catalyst. The recommended procedure is to discard the catalyst after an unsuccessful hydrogenation attempt and try again with fresh catalyst. One or two successive treatments with fresh catalyst and hydrogen under pressure suffice to remove the poison and the desired reduction will take place on the next attempt.

This method of poison removal might also work on the direct hydrogenolysis of the carbinol to 2-(3,5-dimethoxyphenyl)-3-methyloctane.



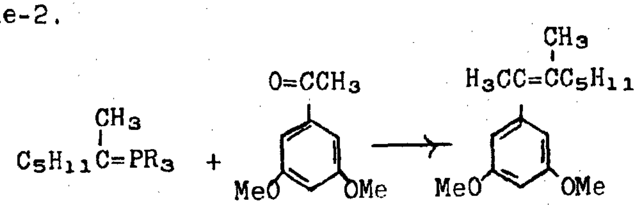
5. <u>2-(3,5-Dihydroxyphenyl)-3-methyloctane (I)</u> 2-(3,5-Dimethoxyphenyl)-3-methyloctane was treated with 48% hydrobromic acid in glacial acetic acid according to the Army Chemical Center's procedure, a modification of the method of Suter and Weston(85). The procedure permitted recovery of uncleaved starting material. The yield of cleaved product was 90% (98.5 area-% pure by VPC), with a conversion of 78%.

A sample of this product, 2-(3,5-dihydroxyphenyl)-3-methyloctane, I, bp 154°C/0.23 mm, was delivered to the Army Chemical Center on 19 January 1962.

B. WITTIG ROUTE TO 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE (I)

The Wittig route was abandoned as being of no further practical interest because it was based on an expensive starting material and because two key reactions failed to take place to a reasonable extent.

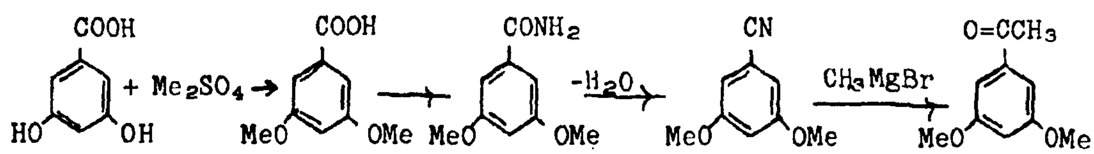
The route was based on the preparation of 3,5-dimethoxyacetophenone and the Wittig reagent from 2-bromoheptane and their expected reaction to form the important olefin, 2-(3,5-dimethoxyphenyl)-3-methyloctene-2.



1. Preparation of 3,5-Dimethoxyacetophenone

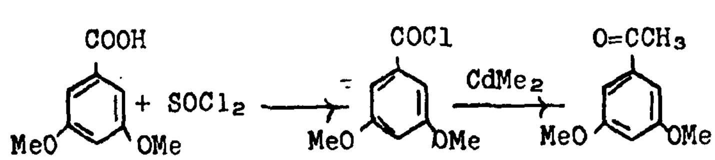
a. From 3,5-Dimethoxybenzonitrile In the laboratory, the most convenient preparation of the acetophenone was from the corresponding nitrile, supplied for this work by the Chemical Corps. The ultimate source of the nitrile is 3,5-dihydroxybenzoic acid, which would be an expensive starting material.

3,5-Dihydroxybenzoic acid was methylated. The resulting 3,5-dimethoxybenzoic acid was converted to the amide and dehydrated to the nitrile. The nitrile was reacted with methylmagnesium bromide to form the desired 3,5-dimethoxyacetophenone by a published procedure[11] in a 64% yield.



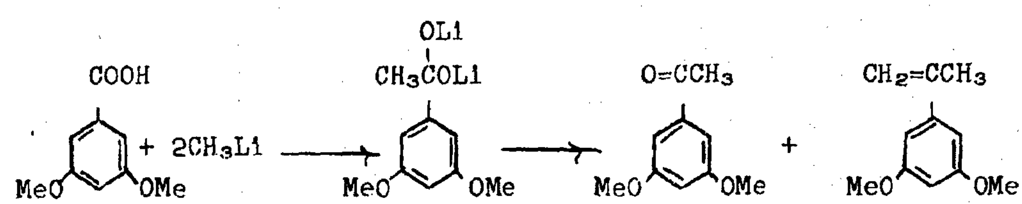
b. <u>From 3,5-Dimethoxybenzoyl Chloride</u> This was a more involved procedure and would probably not have been suitable for large-scale production because of problems associated with the organocadmium reagent required.

3,5-Dihydroxybenzoic acid was methylated with dimethyl sulfate to form[58] 3,5-dimethoxybenzoic acid. This was converted to its acid chloride with thionyl chloride by the method of Munch-Petersen[59] in an 87% yield. The acid chloride was reacted with dimethyl cadmium according to the general procedure of Cason and coworkers[18] in 64% yield.



c. <u>Via Methyl Lithium</u> This procedure was less satisfactory because of low yields.

Methyl lithium was reacted directly with 3,5-dimethoxybenzoic acid in an attempt to make the acetophenone, but the highest yield attained was only 35% (by VPC). 3,5-Dimethoxy-α-methylstyrene was also obtained as a by-product.



Extra precautions such as smaller metal particle size, use of a Dry Ice condenser to avoid loss of iodomethane during methyl lithium formation, and the use of inverse addition, did not improve the yield.

2. <u>Quaternization</u>

The sequence of reactions desired was the reaction of 2-bromoheptane with a trisubstituted phosphine to give a quaternary phosphonium bromide that would be dehydrobrominated with butyl lithium to give the ylene.

$$C_5H_{11}\overset{Br}{\overset{|}{C}}HCH_3 + PR_3 \longrightarrow [C_5H_{11}\overset{CH_3}{\overset{|}{C}}HPR_3]^+ Br^- \xrightarrow{LiC_4H_9} C_5H_{11}\overset{CH_3}{\overset{|}{C}}=PR_3$$

The large amount of premature dehydrobromination accompanying the quaternization step was the main reason for abandoning further work on the Wittig route.

a. <u>2-Bromoheptane</u> 2-Bromoheptane was prepared in two steps from hexanal by treatment with methylmagnesium bromide to produce 2-heptanol, which was then treated with phosphorus tribromide. The respective yields were 87% and 88%.

$$C_5H_{11}CHO + CH_3MgBr \longrightarrow C_5H_{11}\underset{}{\overset{OH}{\overset{|}{C}}}HCH_3 \xrightarrow{PBr_3} C_5H_{11}\text{-}\overset{Br}{\overset{|}{C}}HCH_3$$

Later it was possible to purchase the bromide directly.

b. <u>The Competition between Quaternization and Dehydrobromination</u> Wittig reactions are normally run with triphenylphosphine as the trisubstituted phosphine. Since this reagent is relatively expensive, it is a severe disadvantage that the final oxidation product, triphenylphosphine oxide, cannot be reduced back to triphenylphosphine and recycled. For this reason, some of the experiments were run on tributylphosphine. Tributylphosphine oxide can be reduced and recycled.

Isolation of heptene-1 and heptene-2 from attempted quaternization reactions demonstrated that the following competition was taking place.

$$R_3P + CH_3\overset{Br}{\overset{|}{C}}HCH_2C_4H_9 \longrightarrow \left[R_3\overset{+}{P}\overset{CH_3}{\overset{|}{C}}HC_5H_{11}\right] Br^-$$

$$R_3P + CH_3\overset{Br}{\overset{|}{C}}HCH_2C_4H_9 \longrightarrow [R_3\overset{+}{P}H]Br^- + CH_3CH{=}CHC_4H_9$$

(also + $CH_2{=}CHCH_2C_4H_9$)

The experimental results are summarized in Table 3.

Table 3

WITTIG REACTION INVESTIGATION;

QUATERNIZATION VS DEHYDROBROMINATION

Phosphine	Temperature, °C Bath	Temperature, °C Pot	Time (hr)	Extent of Reaction, %	Amount of Heptenes, %
Bu_3P	160	155‡	3.5	100	min. 66
Bu_3P	130	119‡	3.0	100	not determined
Bu_3P	105-110	95-100	35.0	ca. 100	55
Bu_3P	65-75	60-70	160.0	93	37
$(C_6H_5)_3P$	160-165	150-155	20.0	95	27
$(C_6H_5)_3P$ ≠	-	120-130	113.0	33	5-10 (approx.)

≠ Toluene used as a solvent.

‡ When this temperature was reached there was sudden, vigorous reflux, followed by drop in the pot temperature to 100°.

The heptene formation was not due to simple thermal decomposition of the alkyl bromide since the heating of 2-bromoheptane at 110-120°C for 66 hours resulted only in recovery of the halide. VPC indicated that no heptene was formed.

Lowering the reaction temperature favors the desired reaction; however, with tributylphosphine, the amount of heptene formed even at lower temperatures was still too high to make its use practical in the synthetic scheme under investigation. With triphenylphosphine, lower temperatures gave almost exclusively the desired reaction, but the reaction time required to obtain complete quaternization would be prohibitive on anything other than a very small scale, even if the desired product were formed in the subsequent step. Comparison of the use of the two phosphines in the reaction indicates that much more dehydrobromination is observed with tributylphosphine than with triphenylphosphine. This is not unexpected in view of the basicities of the two materials [pK_a of Bu_3P is 8.4 vs pK_a of ϕ_3P of 2.73[39]]

3. Ylene Formation and the Attempted Wittig Step

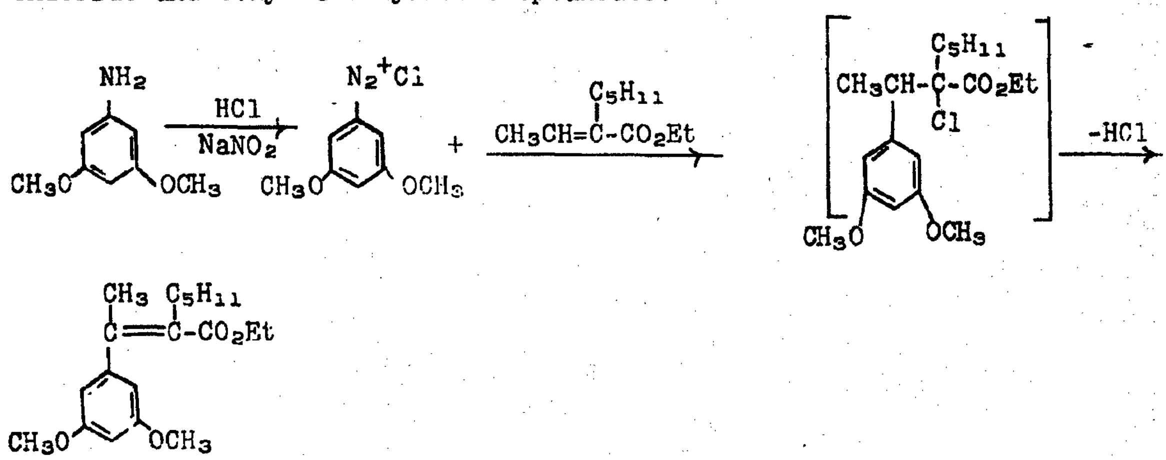
After the premature dehydrobromination was understood, a final attempt at ylene formation and reaction with 3,5-dimethoxyacetophenone was made. Careful examination of the final reaction mixture on a high-temperature vapor phase chromatograph showed no significant quantity of product with the retention time of either of the two isomers of the authentic 2-(3,5-dimethoxyphenyl)-3-methyloctene-2.

The conclusion is unavoidable that attempts to make the desired intermediate via the Wittig reaction have been unsuccessful and offer no promise, as far as can be seen.

C. THE MEERWEIN REACTION ROUTE TO 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE (I)

The Meerwein reaction is the arylation of olefins with diazonium salts with the evolution of nitrogen. The halogen is usually lost and in most cases the product isolated is the olefin. The reaction has been recently reviewed[74].

The application of this reaction that was proposed for the present problem was the reaction of 3,5-dimethoxyphenyldiazonium chloride and ethyl 2-ethylideneheptanoate.



This reaction was run once, but was unsuccessful. The unsaturated ester was tried first because it was most readily obtained, but a much more reactive class of olefins are the α,β-unsaturated nitriles[74]. Any future work should involve the use of an α,β-unsaturated nitrile.

1. Preparation of Ethyl 2-Ethylideneheptanoate

a. Ethyl 2-Acetylheptanoate Acetoacetic ester was alkylated with 1-bromopentane to ethyl 2-acetylheptanoate in 59% yield.

$$CH_3\overset{\overset{O}{\|}}{C}CH_2COOEt + C_5H_{11}Br \longrightarrow CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{C_5H_{11}}{|}}{C}HCOOEt$$

The VPC of the product showed three peaks consistent with the assignments given in Table 4.

Table 4

COMPONENTS OF ETHYL 2-ACETYLHEPTANOATE

Retention Time, min.	Area-%	Assignment	
4.1	4	enol with alkyl groups cis	$(HO)(H_3C)C{=}C(COOEt)(C_5H_{11})$
5.5	93	keto form	$CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{C_5H_{11}}{|}}{C}HCOOEt$
7.7	3	enol with alkyl groups trans	$(HO)(H_3C)C{=}C(C_5H_{11})(COOEt)$

The assignment is made on the basis of the following assumptions: the enol form with the alkyl groups cis would be more prone to intramolecular hydrogen bonding between the proton of the hydroxyl group

and the carbonyl group than would the other enol form, so the form with alkyl groups <u>trans</u> would be expected to boil higher than its geometric isomer, or than the keto form, if the intramolecular hydrogen bonding is sufficiently inhibited.

b. <u>Ethyl 2-(1-Hydroxyethyl)heptanoate</u> Ethyl 2-acetylheptanoate was catalytically reduced to the desired hydroxyester in 94% yield.

$$CH_3CO\overset{C_5H_{11}}{\overset{|}{C}}HCOOEt + H_2 \longrightarrow CH_3\underset{OH}{\underset{|}{C}}H\overset{C_5H_{11}}{\overset{|}{C}}HCOOEt$$

Although the infrared spectrum of this compound was quite consistent with the proposed structure, the VPC showed two major components:

Retention Time, min.	Area-%	Assignment
1.5	1.2	-
2.4	4.7	Ethyl 2-acetylheptanoate (starting material)
3.1	42.1	
3.4	52.0	

The 3.1- and 3.4-minute peaks were incompletely resolved, so their proportions relative to one another could not be measured exactly. They are, at least, of approximately equal concentration.

Examination of the structure of ethyl 2-(1-hydroxyethyl)-heptanoate, $CH_3-\underset{*}{\overset{HO}{\overset{|}{C}}}H-\underset{*}{\overset{C_5H_{11}}{\overset{|}{C}}}H-COOEt$, shows that the compound contains two dissimilar asymmetric centers and thus would exist as two <u>dl</u> pairs.

The ratio of intramolecular and intermolecular hydrogen bonding between the hydroxyl proton and the carbonyl oxygen again plays a

part. It can be shown that the two dl pairs would have different possible conformations with respect to this hydrogen bonding possibility. VPC would not be expected to resolve enantiomorphs in either pair but might very well have separated the two pairs.

c. Ethyl 2-Ethylideneheptanoate Ethyl 2-(1-hydroxyethyl)-heptanoate was recovered unchanged, no dehydration to any unsaturated ester having taken place when the mild dehydrating agents, dry hydrogen chloride, iodine in refluxing benzene, and fused potassium acid sulfate, were used.

When the stronger agents, phosphorus pentoxide and phosphorus oxychloride, were used, dehydration to the desired α,β-ester occurred, accompanied by varying amounts of the β,γ-ester, ethyl 2-vinylheptanoate.

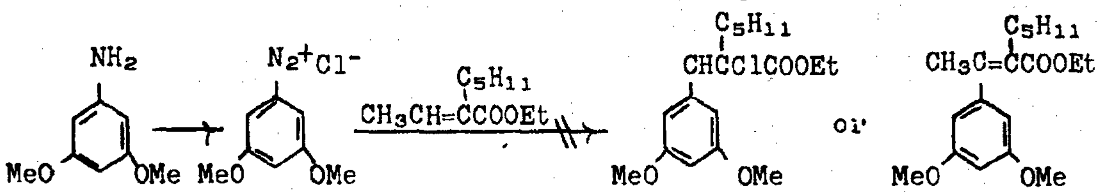
$$\underset{\substack{|\\ OH}}{CH_3CH}\overset{\substack{C_5H_{11}\\ |}}{CH}COOEt \quad -H_2O \longrightarrow CH_3CH{=}\overset{\substack{C_5H_{11}\\ |}}{C}COOEt \quad + \quad CH_2{=}CH\overset{\substack{C_5H_{11}\\ |}}{CH}COOEt$$

Et 2-ethylidene-heptanoate "α,β-ester"	Et 2-vinylhepta-noate "β,γ-ester"

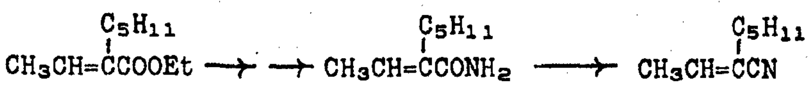
The ethyl 2-vinylheptanoate was successfully eliminated from the products by running the dehydration with phosphorus oxychloride in pyridine. This reagent pair introduced two new components, which turned out to be the two dl pairs of ethyl 2-(1-chloroethyl)heptanoate. The final solution was to dehydrate with phosphorus oxychloride in pyridine and then treat the mixture with the stoichiometric quantity of ethanolic potassium hydroxide. Distillation of the resulting reaction mixture resulted in the isolation of ethyl 2-ethylidene-heptanoate in greater than 98 area-% purity. The overall yield, based on the starting ethyl 2-(1-hydroxyethyl)heptanoate, was 76%.

d. <u>Attempted Meerwein Reaction</u> The preparation of 3,5-dimethoxyaniline by the benzyne reaction on 1-chloro-2,4-dimethoxybenzene has been discussed earlier, section II.A.1.c.

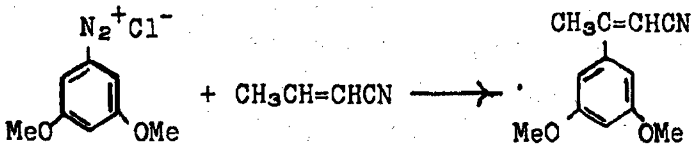
The reaction of 3,5-dimethoxyphenyldiazonium chloride with ethyl 2-ethylideneheptanoate in aqueous acetone using cupric chloride as a catalyst resulted in recovery of 86% of the starting unsaturated ester. It appears that diazo resins were the principal products of the reaction.



The unsaturated ester was tried for the first attempt with the Meerwein route because it was the most easily obtained. A much more reactive class of olefins is the α,β-unsaturated nitriles(8). A future attempt with the Meerwein reaction could involve the use of 2-ethylideneheptanonitrile, which could be prepared from ethyl 2-ethylideneheptanoate:



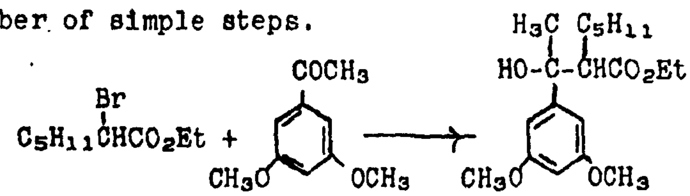
To test whether this approach has any promise at all, a model experiment could be conducted with crotononitrile.



D. REFORMATSKY REACTION ROUTE TO 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE(I)

The Reformatsky reaction is the reaction between zinc, an α-bromoester, and an aldehyde or ketone resulting in the formation of a β-hydroxyester. The reaction has been reviewed[80].

The Reformatsky route to the desired resorcinol depends on the reaction of ethyl 2-bromoheptanoate and 3,5-dimethoxyacetophenone to form ethyl 2-amyl-3-hydroxy-3(3,5-dimethoxyphenyl)butyrate, an intermediate that could be converted to the desired resorcinol by a number of simple steps.

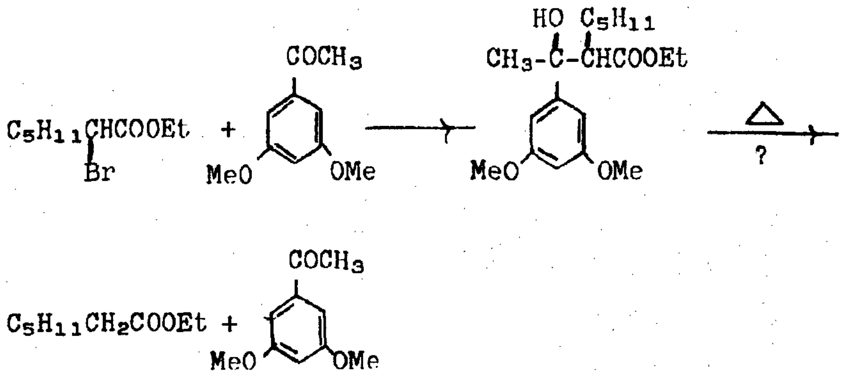


The preparation of 3,5-dimethoxyacetophenone had already been studied during the work on the Wittig route.

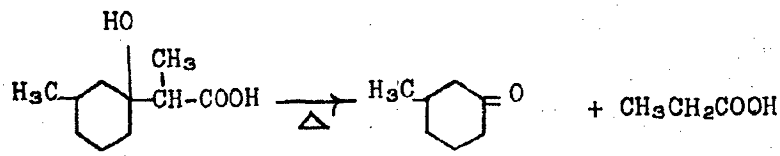
Ethyl 2-bromoheptanoate was purchased directly.

The reaction between ethyl 2-bromoheptanoate and 3,5-dimethoxyacetophenone was carried out once with apparently negative results, as it appeared that the starting materials were recovered on distillation of the reaction mixture, but on re-examination of the reaction products, it was established by VPC that the recovered ester had a distinctly lower retention time than the starting ethyl 2-bromoheptanoate.

Since the literature indicates that in some cases β-hydroxyesters undergo cleavage on heating rather than dehydration, it is considered possible that ethyl 2-amyl-3-hydroxy-3(3,5-dimethoxyphenyl)-butyrate was actually formed and decomposed on distillation to 3,5-dimethoxyacetophenone and ethylheptanoate.



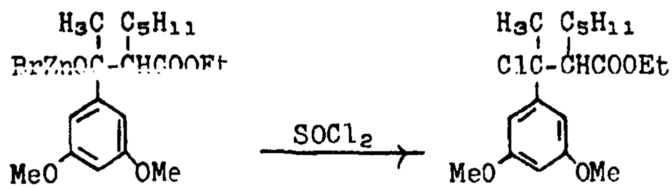
An example(93) of this type of decomposition would be that of α-(1-hydroxy-3-methylcyclohexyl)propionic acid.



Such a course appears reasonable in view of the observations made during distillation of the crude product. The distillation resulted in two small fractions, one of which was an ester and the other 3,5-dimethoxyacetophenone. The main fraction was very high boiling: 150-160°C/0.4 mm. Redistillation of the high-boiling fraction resulted in larger amounts of the ester and ketone and a smaller high-boiling cut. Each subsequent distillation had the same result. From this it appears that the distillation was resulting in decomposition. VPC's on the crude product before distillation were inconclusive since the column temperature required, 310°C, also caused decomposition. However, even with this decomposition, a component with a retention time that was reasonable for the desired

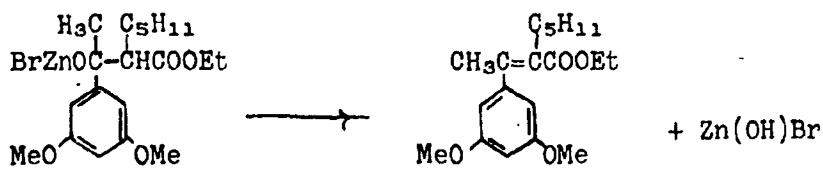
ethyl 2-amyl-3-hydroxy-3(3,5-dimethoxyphenyl)butyrate was shown to be present in 26 area-%.

This decomposition could be circumvented by conversion of the halozinc intermediate to a chloride without hydrolysis(10).

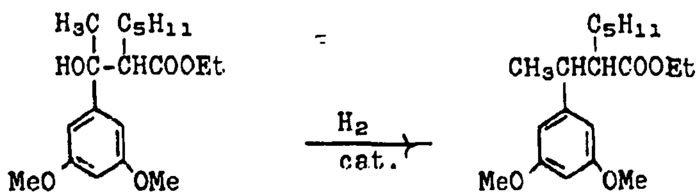


The chloride could be dehydrohalogenated or hydrogenolyzed.

Alternatively, the halozinc intermediate could be dehydrated before hydrolysis(80).

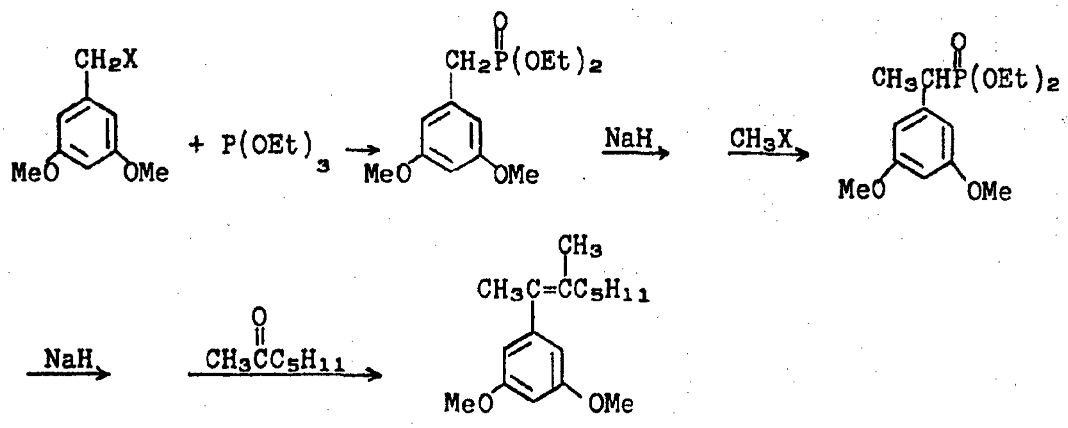


Finally, the crude alcohol could be hydrogenolyzed at temperatures below the decomposition point.



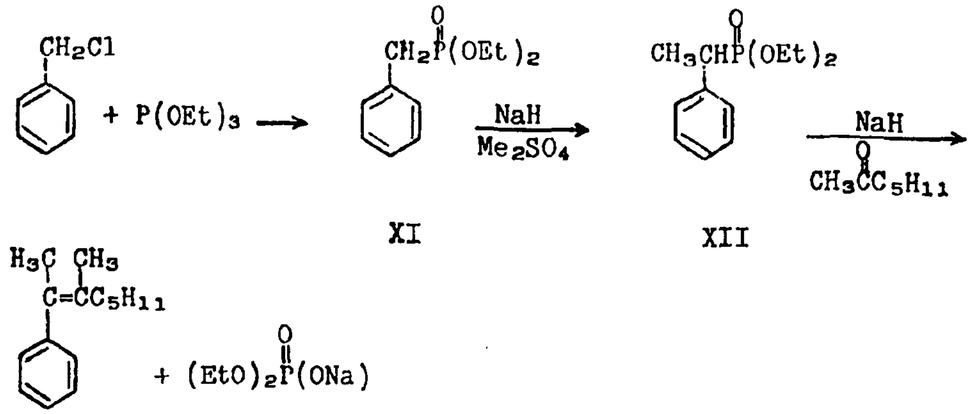
E. PHOSPHONATE CARBANION ROUTE TO 2-(3,5-DIHYDROXYPHENYL-3-METHYLOCTANE (I)

The route started from 3,5-dimethoxybenzyl halide, which would be reacted with triethyl phosphite. The resulting phosphonate carbanion was methylated and added to 2-heptanone. The addition of phosphonate carbanions to carbonyl compounds has recently been described by Horner and coworkers(44) and by Wadsworth and Emmons in this country(92).



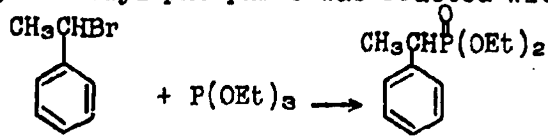
The investigation had three separate phases: (1) the alkylation of the phosphonate carbanion; (2) the application of the olefin synthesis for the introduction of the desired side-chain; and (3) the preparation of 3,5-dimethoxybenzyl halide, for which no economical preparation was available.

1. Diethyl 1-Phenylethylphosphonate Introduction of the side-chain was investigated using an unsubstituted benzyl halide as a model compound since the two methoxy groups should have little or no effect on the olefin synthesis. The following sequence was investigated:



XI XII

Diethyl benzylphosphonate, XI, was prepared in 97% yield by the reaction of benzyl chloride with triethyl phosphite. This product was then treated with sodium hydride and dimethyl sulfate in 1,2-dimethoxyethane at 60°C. An exothermic reaction took place and hydrogen was evolved. Since the desired product, diethyl 1-phenylethylphosphonate, XII, and the starting material differ by only a methyl group, it was felt that separation by distillation would be impossible and the reaction would have to be quantitative to be of any value. In order to have an authentic sample of XII for comparison, triethyl phosphite was reacted with (1-bromoethyl)benzene.



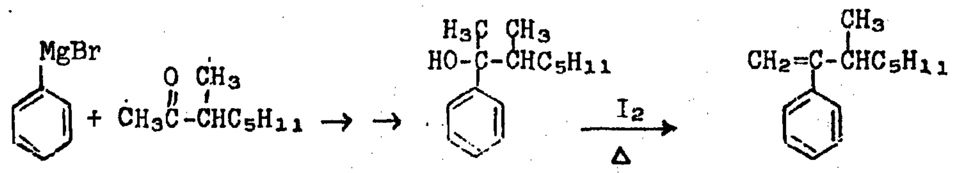
Samples of diethyl benzylphosphonate and the methylated product prepared by the two different routes were compared, but the differences in boiling point, refractive index, and retention time were too small to demonstrate that reaction had taken place quantitatively. Later, VPC conditions were worked out that gave resolution of XI and XII. Under these conditions, VPC showed that the methylation had only proceeded to the extent of 25%.

As another model reaction, a butylation of XI was carried out, using dibutyl sulfate, which had been prepared by the <u>Organic Synthesis</u> procedure(84). This resulted in an 82% yield of diethyl 1-phenylamylphosphonate having a retention time readily distinguishable from that of the unalkylated diethyl benzylphosphonate (19.5 minutes compared with 9.2 minutes).

The reason for the contrast between the 82% yield on butylation and the 25% yield on the desired methylation is not known.

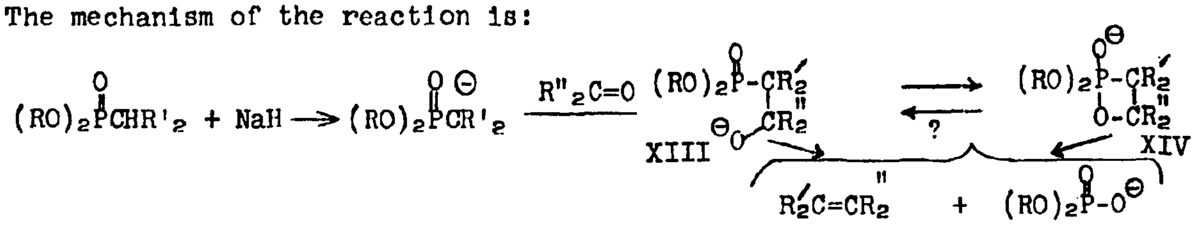
2. <u>Attempted Preparation of 2-Phenyl-3-methyloctene-2</u>

Before investigating the alkylation further, the olefin-producing step was studied because if it failed, this entire route would have to be abandoned. In order to have an authentic sample of 2-phenyl-3-methyloctene-2 for comparison, phenylmagnesium bromide was reacted with 3-methyloctanone-2 and the resulting alcohol dehydrated. However, VPC and infrared analyses indicated the product to be largely the terminal olefin, 2-phenyl-3-methyloctene-1, instead of the desired internal olefin.

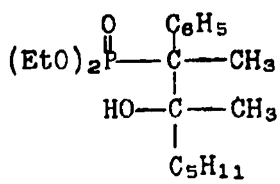


The diethyl 1-phenylethylphosphonate used in this work was prepared from 1-phenylethyl bromide and triethyl phosphite as outlined above and was greater than 99 area-% pure by VPC.

The reaction of this phosphonate with 2-heptanone and sodium hydride in 1,2-dimethoxyethane was carried out twice following the literature procedure[92]. The reaction proceeded as described, but on work-up, the residue obtained would not distil at 125°C/0.3 mm. The desired 2-phenyl-3-methyloctene-2 should boil at about 80°C/0.3 mm. After looking at the mechanism proposed for olefin formation, a possible reason for failure in this case was considered. The mechanism of the reaction is:



While previous workers[44,92] used generalized equations, they did not show any examples that led to tetra-substituted olefins. In our case one R'- is phenyl and the other methyl, and one R"- is methyl and the other amyl. This might mean that in this instance, for steric reasons, XIII could not assume the spatial arrangement necessary for breakdown to the desired products or, if the reaction proceeds through a four-center transition state as shown in XIV, that the steric requirements of the groups involved prevent its formation. This would mean that the reaction would stop at XIII and hydrolysis in the work-up would lead to



XV

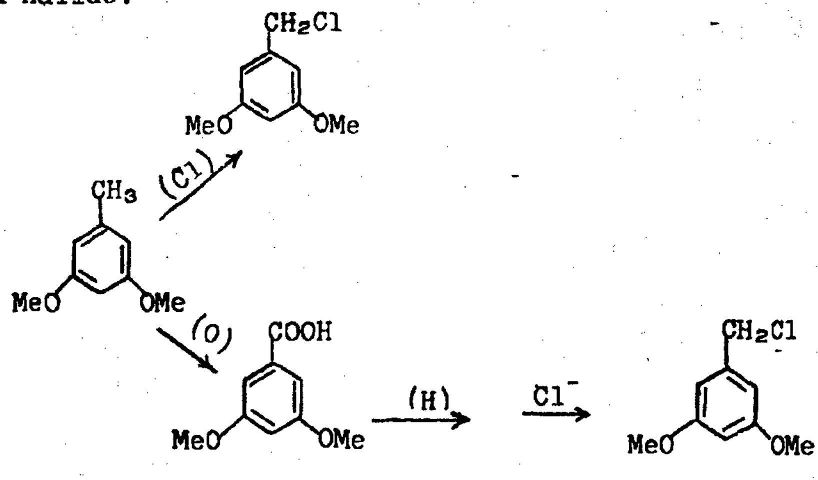
which would be a high-boiling liquid. It is interesting to note that when this reaction is carried out in a proton-donating solvent, products of the type represented by XV are obtained[63].

In an attempt to decompose an intermediate such as XV, the reaction was rerun at a higher temperature with identical negative results.

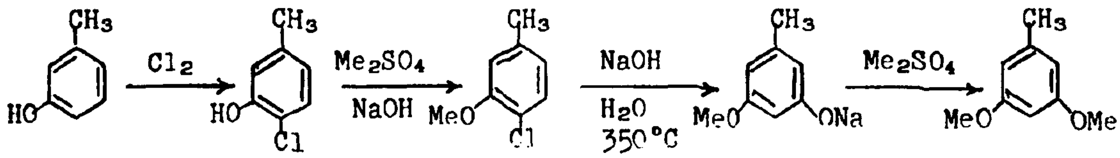
Olefin synthesis by the phosphonate carbanion reaction may not be feasible in this instance.

3. Attempted Preparation of Orcinol from 4-Chloro-m-cresol

The final phase of this route is the de elopment of a practical route to 3,5-dimethoxybenzyl halide. 3,5-Dimethoxytoluene (the dimethyl ether of orcinol) might be a useful intermediate since it might undergo side-chain chlorination to form the desired benzyl halide directly or it could be converted by oxidation to 3,5-dimethoxybenzoic acid, which could then be converted to the desired halide.

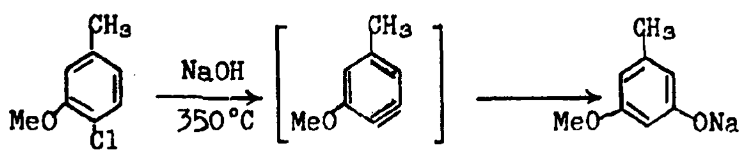


In order for these preparations of 3,5-dimethoxybenzyl chloride to have a practical value, an inexpensive route to orcinol dimethyl ether would be necessary. A scheme was devised starting from m-cresol at 60 cents/lb, as outlined below.



The first step was not carried out in the laboratory since it was possible to purchase 4-chloro-m-cresol. The second step was carried out and resulted in a 92% yield of 3-methoxy-4-chlorotoluene.

The critical step is the third step, which is an aqueous benzyne reaction. Bottini and Roberts(16) have investigated the liquid phase hydrolysis of halotoluenes and found that at 350°C the mechanism of reaction involves a benzyne intermediate. Since previous workers(47) have shown that the reaction of 3-methoxybenzyne intermediates gives exclusively m-disubstitution products, it seems reasonable to assume that the basic hydrolysis of 3-methoxy-4-chlorotoluene under benzyne conditions might lead to the desired product.



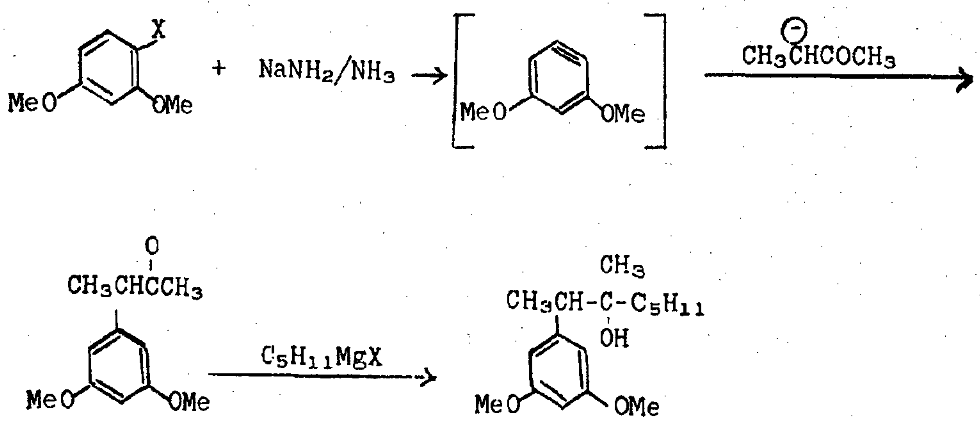
The reaction of 3-methoxy-4-chlorotoluene with 4M sodium hydroxide at 340-350°C for two hours in an autoclave resulted in a 46% yield of m-cresol as the only identifiable product.

4. Conclusions on the Phosphonate Carbanion Route

None of the three phases of the investigation of this route gave favorable results. The alkylation of the phosphonate carbanion with a methyl group gave a very poor yield, the olefin synthesis step was unsuccessful, and one scheme to prepare the 3,5-dimethoxybenzyl halide failed. Each of these three phases would have to be satisfactory for the route to be feasible.

F. ROUTE TO 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE (I) VIA DIRECT RESORCYLATION OF BUTANONE

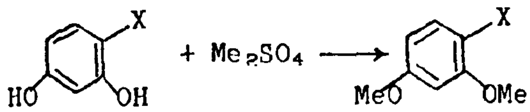
This route depends on the formation of the anion from butanone by a strong base and its interaction with the benzyne derived from 1-halo-2,4-dimethoxybenzene. The resulting ketone would be reacted with amyl Grignard to form a carbinol precursor of the desired intermediate.



1. Preparation of 1-Halo-2,4-dimethoxybenzene Starting Materials

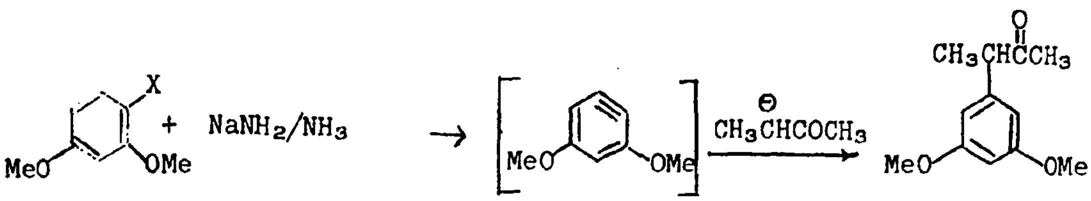
The preparation of 1-chloro-2,4-dimethoxybenzene from 4-chlororesorcinol was repeated on a 4.4-mole scale. The yield was 78%.

1-Bromo-2,4-dimethoxybenzene was prepared from 4-bromoresorcinol by the same route on a 0.5-mole scale, in 71% yield.



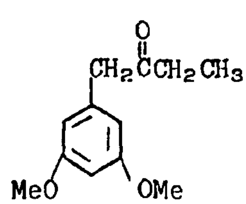
2. Attempted Resorcylation Reactions in Liquid Ammonia

Six attempts were made to prepare 3-(3,5-dimethoxyphenyl)-butanone-2 by the resorcylation reaction(52) in the liquid ammonia system.



The results are summarized in Table 5. It is apparent that the reaction has proved unsatisfactory. Only trace quantities of the desired ketone have been isolated. Unfortunately, the major reaction product has been found to be 3,5-dimethoxyaniline, which results from the attack of amide ion on the transient benzyne intermediate.

Concern about the possibility of reaction at the wrong point on the butanone chain proved to be justified. Examination of the products of these runs with programmed VPC revealed the presence of 1-(3,5-dimethoxyphenyl)butanone-2, XVI, in trace amounts relative to the desired 3-(3,5-dimethoxy)butanone-2.



XVI

Table 5

RESORCYLATION REACTIONS IN THE LIQUID AMMONIA SYSTEM

	Experiment No. 1	2	3	4	5	6
Reaction Conditions						
Two-flask procedure	X	X	X			
One-flask procedure				X	X	X
Reaction time, min.	15	90	10	30	30	15
Starting Materials						
1-Chloro-2,4-dimethoxybenzene, moles	0.25	0.25	0.25	0.25		0.25
1-Bromo-2,4-dimethoxybenzene, moles					0.25	
Butanone, moles	0.50	1.25	1.00	0.75	0.75	0.50
Sodamide, moles	1.00	1.50	1.50	1.25	1.25	1.00
Liquid ammonia, ml	1200	2400	1400	600	600	800
Reaction Products						
3-(3,5-Dimethoxyphenyl)butanone-2 (desired product) % yield	1	0	2	4	4	3
3,5-Dimethoxyaniline, % yield	38	0	30	32	65	42
1-Halo-2,4-dimethoxybenzene, recovered starting material, % yield	37	98	59	46	23	49

a. Experiment No. 1   This reaction was carried out using the stoichiometry and reaction conditions found by Leake and Levine[52] to be most favorable in forming 3-phenylbutanone-2 from bromobenzene and butanone.

b. Experiment No. 2   Just sufficient sodamide was used in this run to generate the benzyne and the ketonic carbanion. It is significant that apparently no benzyne formed, since no trace of 3,5-dimethoxyaniline could be detected in reaction product. This suggests that it is necessary to have sodamide in excess of the amount theoretically needed to dehydrohalogenate the 1-halo-2,4-dimethoxybenzene and promote subsequent reaction.

c. Experiments No. 4 and 5   These runs were carried out under identical conditions, except that in experiment 5, 1-bromo-2,4-dimethoxybenzene was substituted for its chloro analog. The bromo compound was found to form the benzyne more readily and to a greater extent than the chloro compound. Unfortunately, this is manifested in increased yield of the aniline and not of the desired reaction product.

d. Experiment No. 6   This run was carried out via the one-flask method also described by Leake and Levine[52].

e. Interpretation of Results   Recent consultation with Dr. Robert Levine, whose original work on the phenylation of active hydrogen compounds suggested this route, revealed the following discouraging information.

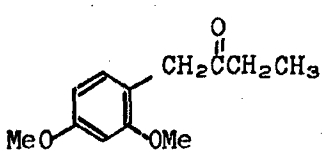
Substitution of the benzyne with methoxyl groups appears to favor the formation of the aniline derivative at the expense of

the desired product derived from the ketone anion. Thus, reaction of the benzyne derived from bromobenzene with the anion from butanone led to the isolation of 75% yields of 3-phenylbutanone-2[52], but when the benzyne source was o-bromoanisole, the yield of phenylated ketones dropped to between 15 and 20%, and the major reaction product was found to be m-anisidine[75]. The results reported here for the benzyne substituted with two methoxyl groups are consistent with that trend.

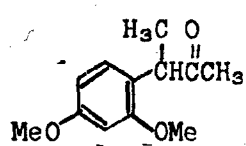
3. Attempted Resorcylation Reaction in Diglyme

The reaction was carried out in the same manner, except that diglyme was substituted for liquid ammonia as the reaction solvent. The desired 3-(3,5-dimethoxyphenyl)butanone-2 was formed in only 3% yield, 3,5-dimethoxyaniline was absent, and 71% of the starting halide was recovered.

In addition to the desired ketone, two other ketones were formed in trace amounts. Infrared spectra indicated these ketones to be 1-(3,5-dimethoxyphenyl)butanone-2 (XVI) and either 1-(2,4-dimethoxyphenyl)butanone-2 (XVII), or 3-(2,4-dimethoxyphenyl)-butanone-2 (XVIII).



XVII



XVIII

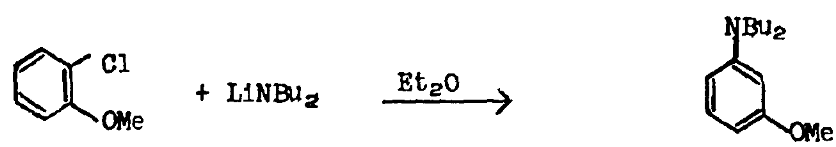
Compound XVI results from resorcylation on the active methyl group of butanone; while XVII or XVIII result if reaction proceeds by direct substitution.

In summary, the use of diglyme as a solvent for resorcylation reactions was ineffective. Apparently direct substitution occurs to a small degree in this solvent.

4. Use of Lithium Alkyl Amides

In most cases in the liquid ammonia system, when reaction took place, the principal product was 3,5-dimethoxyaniline. The benzyne intermediate apparently reacted quite readily with amide ion. It appeared that the use of a base more hindered than amide ion might lead to more favorable results.

Gilman and Kyle[32] have reported the use of lithium dibutylamide in ether on o-chloroanisole to obtain a 48% yield of m-methoxydibutylaniline.

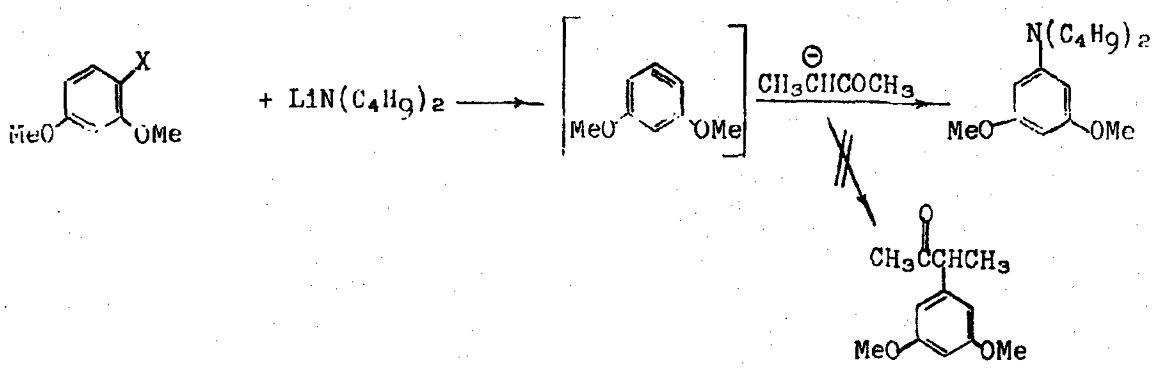


It is interesting to note that lithium dialkylamides react with aryl halides to form N,N-dialkylanilines on a mole-to-mole basis[32,45], while sodamide reacts with aryl halides to form anilines on a 2:1 mole basis. It was hoped that this new approach would eliminate the previously-encountered complication caused by the presence of excess amide ion.

This base-solvent system was applied to the Resorcylation Route, but the results were very disappointing.

The reaction products included recovered 1-chloro-2,4-dimethoxybenzene (41% recovery), a mixture of isomeric ketones (5% yield), a trace of what appeared to be 2,2',4,4'-tetramethoxybiphenyl (coupling

product), and the major reaction product, shown by infrared to be 3,5-dimethoxy-N,N-dibutylaniline in excellent purity and 44% yield. The infrared spectrum of this compound exhibited 1,3,5-substitution on the benzene ring. 3,5-Dimethoxy-N,N-dibutylaniline is a new compound.

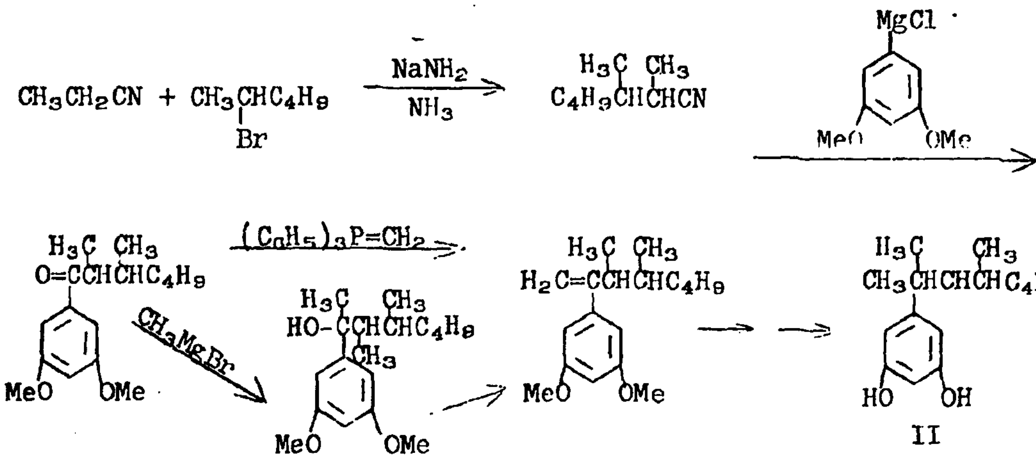


The ketonic portion of the reaction products was composed of four isomeric ketones. VPC was used to trap two of these ketones in good purity, but the remaining two ketones could only be trapped as an unresolved pair. Infrared study of these ketones indicated the presence of a pair exhibiting 1,2,4-substitution on the benzene ring, and a second pair exhibiting 1,3,5-substitution. The first pair would result from direct substitution, and the second pair from attack on a benzyne intermediate. Since the combined yield of isomeric ketones was so low, no effort was made to determine which of the ketones exhibiting 1,3,5-substitution was the desired ketone. VPC and infrared indicated that the 1,2,4-ketones were predominant. The four possible ketones are the desired 3-(3,5-dimethoxyphenyl)butanone-2 and XVI, XVII, and XVIII.

In view of the discouraging results, further investigation of the Resorcylation Route did not seem warranted.

G. SYNTHESIS OF 2-(3,5-DIHYDROXYPHENYL)-3,4-DIMETHYLOCTANE (II)

The synthesis is based on the reaction of 3,5-dimethoxyphenylmagnesium chloride and 2,3-dimethylheptanonitrile:



II

1. 2,3-Dimethylheptanonitrile

Propionitrile was alkylated with 2-bromohexane to result in the isolation of 2,3-dimethylheptanonitrile of 97.1 area-% purity in 51% conversion. Since a portion of the 2-bromohexane was recovered the overall yield was 57%.

2. 2-(3,5-Dimethoxybenzoyl)-3-methylheptane

2,3-Dimethylheptanonitrile was reacted with 3,5-dimethoxyphenylmagnesium chloride to form 2-(3,5-dimethoxybenzoyl)-3-methylheptane in about 50% yield. The presence of two dissimilar asymmetric centers in the product causes the formation of two dl pairs, so VPC results were inconclusive.

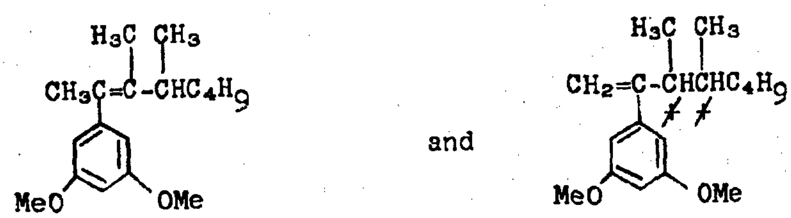
3. 2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctene-1

This compound was originally approached via a Grignard reaction

of the ketone 2-(3,5-dimethoxybenzoyl)-3-methylheptane with methylmagnesium bromide. When the dehydration of the resulting carbinol complicated, the Grignard reaction was replaced by a Wittig reaction of the same ketone with triphenylphosphine methylene.

a. <u>2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctanol-2 by a Grignard Reaction</u> 2-(3,5-Dimethoxybenzoyl)-3-methylheptane was reacted with methylmagnesium bromide to form 2-(3,5-dimethoxyphenyl)-3,4-dimethyloctanol-2, which was separated by distillation but not further characterized.

b. <u>Attempted Dehydration of 2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctanol-2</u> The carbinol was dehydrated by heating with iodine to form, if there was no rearrangement, a mixture of the <u>cis</u> and <u>trans</u> isomers of the internal olefin and the various stereoisomers of the terminal olefin containing two asymmetric centers:



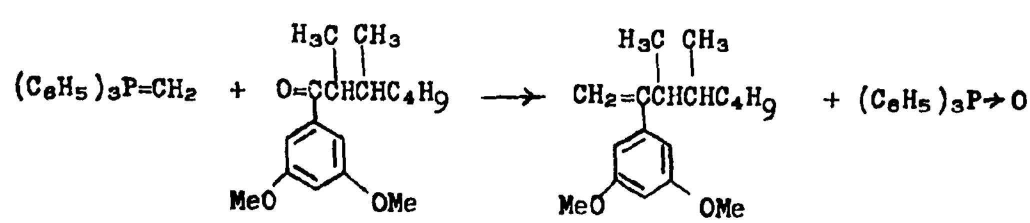
<u>cis</u> and <u>trans</u> 2 <u>dl</u> pairs

VPC was inconclusive since the above mixture could show as many as four components; two arising from the <u>cis</u> and <u>trans</u> forms of the internal olefin and two being the result of the two <u>dl</u> pairs possible for the terminal olefin.

The VPC did show four components; however, none of these showed terminal double bond absorptions in the infrared. From this it must be concluded that, at most, only two of the components represent the desired product. The most likely explanation would be that dehydration of the carbinol was accompanied by isomerization.

In order to circumvent this difficulty it was felt that a method of dehydration had to be found in which no isomerization occurred. The first consideration was given to acetate pyrolysis. The carbinol was never converted to its acetate. Difficulty was encountered in the conversion of the corresponding carbinol to acetate for resorcinol IV (see below) and at that time it was suggested by the Project Officer, Donald H. Wadsworth, that the Wittig reaction on the predecessor ketone be considered for preparation of the olefin.

c. Olefin-formation by the Wittig Reaction The use of the Wittig reaction completely eliminated dehydration and its accompanying isomerization.



The reaction of triphenylphosphine methylene with 2-(3,5-dimethoxybenzoyl)-3-methylheptane resulted in a 53% yield (by VPC) of 2-(3,5-dimethoxyphenyl)-3,4-dimethyloctene-1. The product was contaminated with a small amount (5 to 7 area-%) of unreacted ketone, which was removed by careful fractionation after reduction.

4. 2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctane

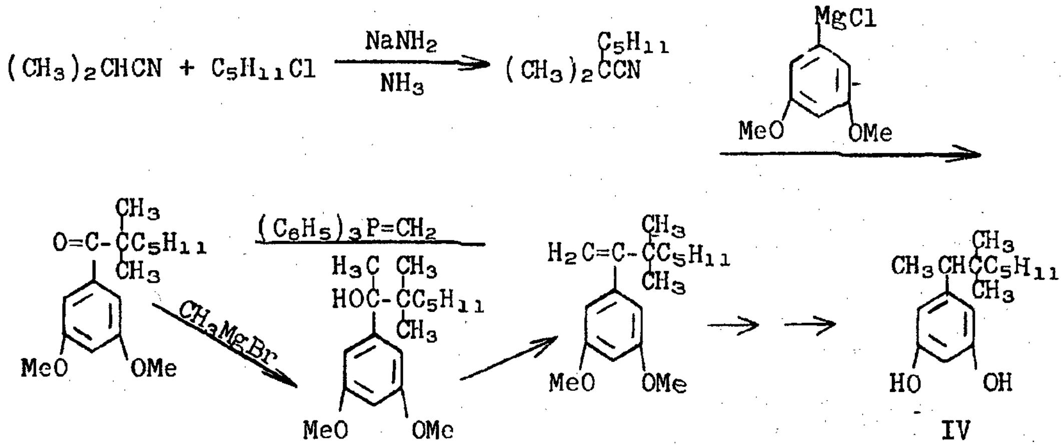
Initial attempts at catalytic reduction of the olefin over nickel-on-kieselguhr were unsuccessful, but use of a higher temperature and a larger amount of fresh catalyst resulted in the isolation of 2-(3,5-dimethoxyphenyl)-3,4-dimethyloctane.

5. 2-(3,5-Dihydroxyphenyl-3,4-dimethyloctane (II)

2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctane was cleaved with 48% hydrobromic acid in glacial acetic acid by the procedure used for resorcinol I (see section II.A.5) to yield the desired resorcinol. A 7.5 g sample of this product, 2-(3,5-dihydroxyphenyl)-3,4-dimethyloctane, II, was shipped to the Army Chemical Center on 5 April 1962. It boiled at 160-161°C/0.3 mm.

H. SYNTHESIS OF 2-(3,5-DIHYDROXYPHENYL)-3,3-DIMETHYLOCTANE (IV)

Similar to the route for resorcinol II, this one is based on the reaction of the same Grignard reagent with 2,2-dimethylheptanonitrile:



IV

1. <u>2,2-Dimethylheptanonitrile</u>

Isobutyronitrile was alkylated with amyl chloride and sodium in liquid ammonia to give a 46% yield of 2,2-dimethylheptanonitrile of 97.2 area-% purity.

2. <u>2-(3,5-Dimethoxybenzoyl)-2-methylheptane</u>

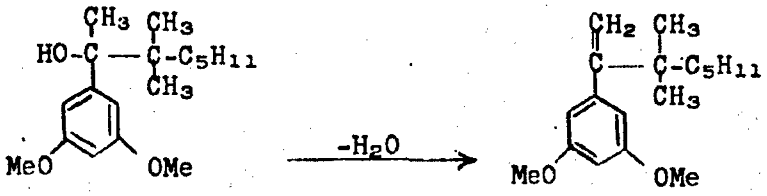
2,2-Dimethylheptanonitrile was reacted with 3,5-dimethoxyphenylmagnesium chloride on 0.4-mole scale resulting in the isolation of 57.8 g of 2-(3,5-dimethoxybenzoyl)-2-methylheptane, bp 134-136°C/0.19 mm, > 98 area-% pure by VPC. The conversion was 53% of theory (71% yield based on nitrile consumed).

3. <u>2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctene-1</u>

As with the analogous olefin in the synthesis of item II, the preparation of this olefin was originally approached via the Grignard reaction of 2-(3,5-dimethoxybenzoyl)-2-methylheptane with methylmagnesium bromide. Again, when the dehydration of the resulting carbinol became complicated, the olefin was prepared by the Wittig reaction of triphenylphosphine methylene on the same ketone.

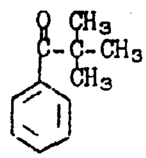
a. <u>2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctanol-2 by a Grignard Reaction</u> 2-(3,5-Dimethoxybenzoyl)-2-methylheptane was reacted with methylmagnesium bromide to form 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctanol-2. This carbinol was separated by distillation but was not further characterized because of decomposition on attempted investigation by VPC.

b. <u>2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctenes by Iodine Dehydration</u> The best distillation cut of the carbinol, 44 g, bp 139-140°C/0.15 mm, was heated with two small crystals of iodine at 120-135°C for 2.3 hours, and after distillation, 29.4 g (80% yield) of a dehydration product (bp 115.5-116°C/0.2 mm) was obtained. VPC indicated the presence of two major components, 78.1 area-% and 20.2 area-%. This was disturbing since the desired dehydration,



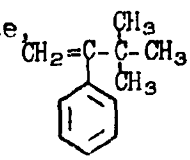
should lead to a single product incapable of <u>cis-trans</u> or stereo isomerism. Infrared indicated that the larger component was a terminal olefin while the smaller was an internal olefin. The 78% component was later identified as the desired 1-olefin by its identity with the product from the Wittig reaction (see section II.H.3.d, below). Before the Wittig reaction was performed, the proper identification of that olefin was complicated by the observation that neither component of this olefin mixture showed the ultraviolet absorption expected for a double bond conjugated with the aromatic ring.

Examination of the literature led to an explanation of the anomolous ultraviolet spectrum. Heddon and Brown[37], investigating the ultraviolet spectrum of pivalophenone,



had found that no conjugation band was present. Their explanation is that in order to observe a conjugation band the double bond has to be coplanar with the ring. In pivalophenone the two methyl groups on the α-carbon displace the carbonyl group out of the plane of the benzene ring and, as a result, resonance is inhibited and no conjugation band appears in the ultraviolet spectrum.

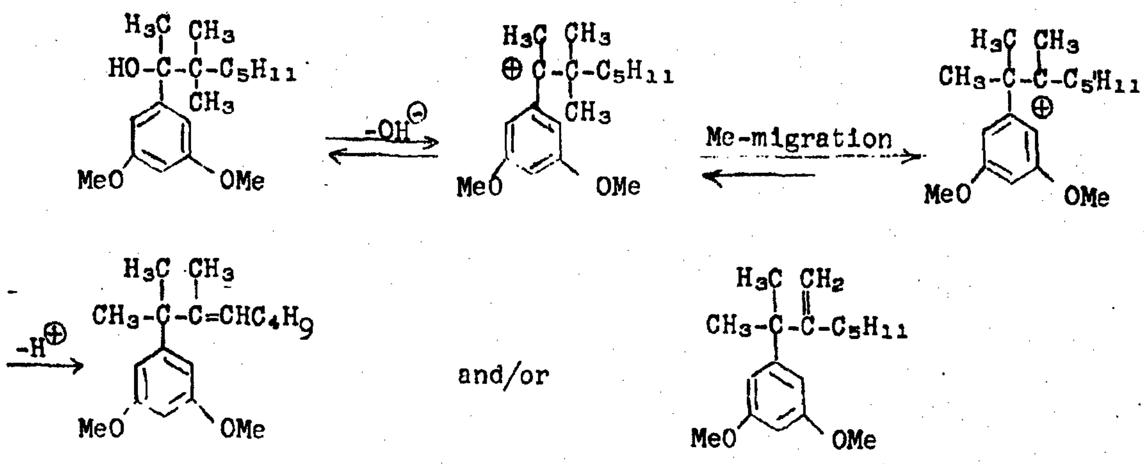
The same absence of a conjugation band was observed in the ultraviolet spectrum of t-butylstyrene,



by Ramart-Lucas[68], who also cited steric inhibition of resonance as the explanation.

In view of the above observations we concluded that the olefin present in 78% was the desired one and that the lack of a conjugation band in the ultraviolet was again due to steric inhibition of resonance. A quaternary carbon atom or its equivalent in bulkiness seems to be necessary for this effect, as steric inhibition of resonance was not noted in the spectra of 2-(3,5-dimethoxyphenyl)-3-methyloctenes (section II.A.4, above) or of 2-(3,5-dimethoxyphenyl)-3-methylheptene-2[1].

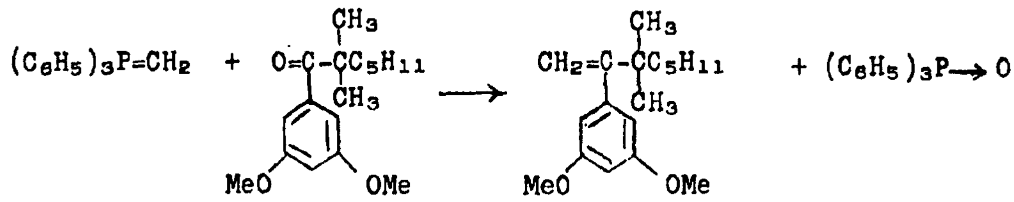
We must further conclude that the dehydration of 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctanol-2 must have led to about 22% rearrangement. A possible rearrangement was the following:



c. <u>Attempted Preparation of 2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctenes by Acetate Pyrolysis</u> To avoid the rearrangement found on iodine dehydration, acetate pyrolysis was considered. 2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctanol-2 was reacted with acetyl chloride and pyridine in dimethoxyethane. Distillation of the reaction mixture resulted in very little product and a very large amount of viscous, high-boiling residue.

At this point the Wittig reaction was suggested as an alternative by Wadsworth and no further work was done on acetate pyrolysis.

d. <u>2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctene-1 by the Wittig Reaction</u> Triphenylphosphine methylene was reacted with 2-(3,5-dimethoxybenzoyl)-2-methylheptane to give a 70% yield of the desired olefin. The major distillation cut was 97 area-% pure. The infrared spectrum was consistent with the structure and the ultraviolet spectrum identical with the anomolous spectrum described above in section II.H.3.b.



4. 2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctane

As with resorcinols I and II, the precursor olefin prepared by the Wittig reaction could not be catalytically reduced on the first attempt. It was successfully reduced to 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctane on the second attempt with a larger amount of fresh catalyst.

5. 2-(3,5-Dihydroxyphenyl)-3,3-dimethyloctane (IV)

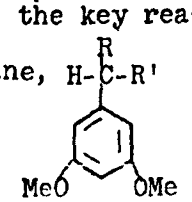
2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctane was cleaved with 48% hydrobromic acid in glacial acetic acid by the procedure used previously for resorcinols I and II, to yield the desired resorcinol.

A 15 g sample of this product, 2-(3,5-dihydroxyphenyl)-3,3-dimethyloctane, IV, was also shipped to the Army Chemical Center on 5 April 1962. It boiled at 154-155°C/0.18 mm.

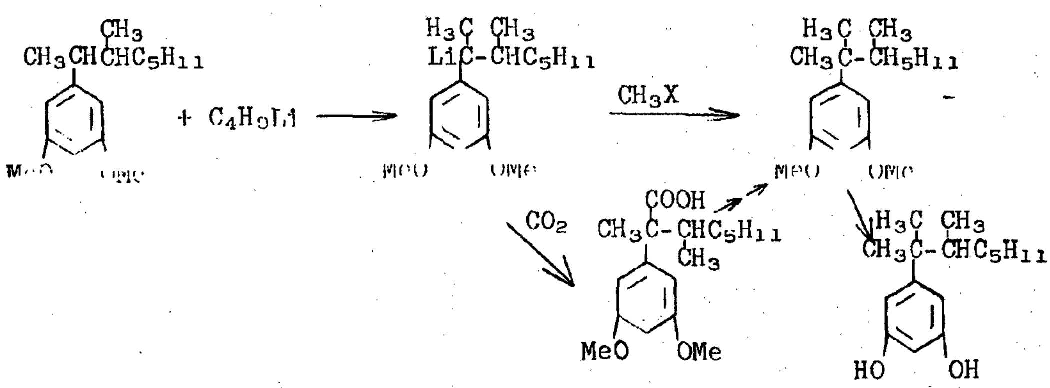
I. ROUTES TO 2-(3,5-DIHYDROXYPHENYL)-2,3-DIMETHYLOCTANE (III), 2-(3,5-DIHYDROXYPHENYL)-2-METHYLHEXANE (VI), AND 2-(3,5-DIHYDROXY-PHENYL)-2-METHYLHEPTANE (VII)

1. Metalation Routes to Resorcinols III, V, VI, and VII

Several routes were suggested for the preparation of resorcinols III, V, VI, and VII in which the key reaction involved the metalation of a 3,5-dimethoxyphenylalkane,

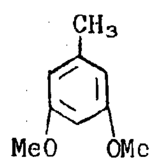


with butyl lithium at the benzyl hydrogen followed by either coupling with methyl halide or carbonation and reduction. An example is the metalation route to resorcinol III:



III

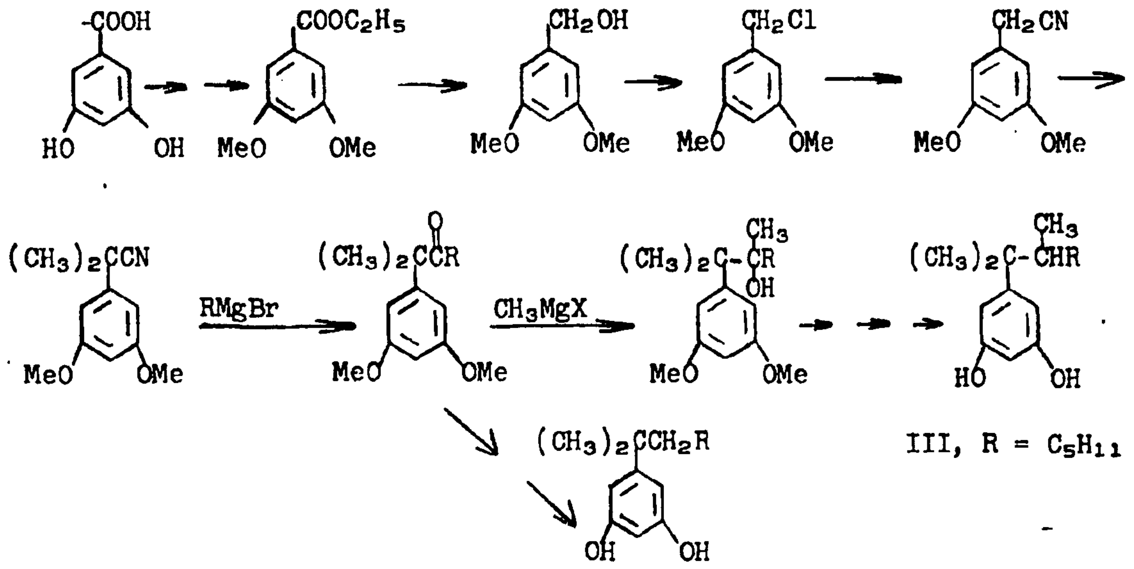
The key assumption in the metalation routes; namely, that a 3,5-dimethoxyphenylalkane could be metalated with butyl lithium on the benzyl carbon atom, has been demonstrated to be false. Adams and co-workers(6) subjected the dimethyl ether of orcinol,



to reaction with both phenyl and butyl lithium and in both cases observed metalation at the 2-position (between the methoxy groups). This was proved by carbonation of the lithium derivative to give the known 2,6-dimethoxy-4-methylbenzoic acid. In view of this report it is extremely unlikely that the proposed metalation routes would have been successful. They were abandoned in favor of the routes via 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile described below.

2. Routes via 2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile

These routes are based, in part, on the work of Adams, MacKenzie, and Loewe(5). They apply only to resorcinols III, VI, and VII, and would not provide a route to V, for which no route is presently available.

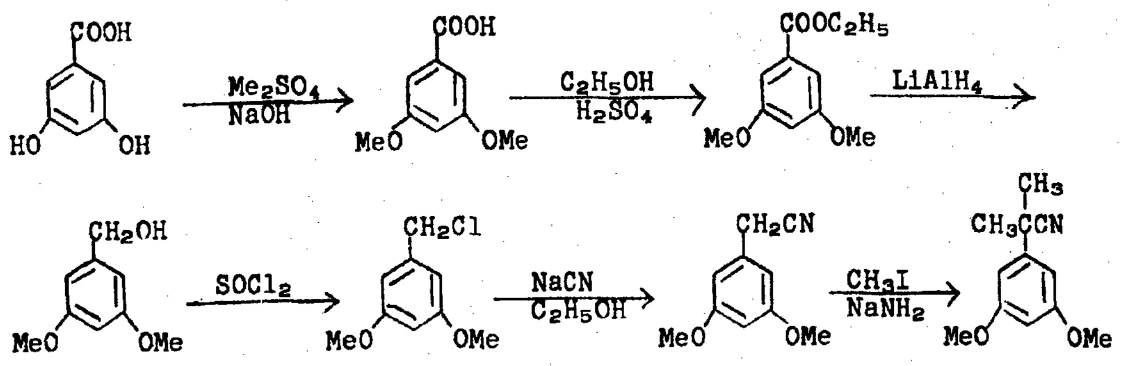


III, R = C_5H_{11}

VI, R = C_3H_7
VII, R = C_4H_9

The common nitrile intermediate was only used in an attempted preparation of 2-(3,5-dihydroxyphenyl)-2-methylheptane, VII. Funds were not available to complete that attempt, or to start work on resorcinols III or VI.

a. 2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile from 3,5-Dimethoxybenzoic Acid Since the program for the preparation of resorcinols III, VI, and VII was merely synthetic and did not require extremely cheap starting materials, it was practical to consider the following rather long route to the common intermediate for resorcinols III, VI, and VII:

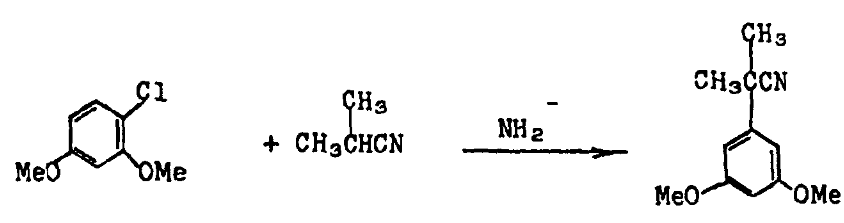


3,5-Dimethoxybenzoic acid was prepared in 84% yield from 3,5-dihydroxybenzoic acid, dimethyl sulfate, and sodium hydroxide following a procedure outlined previously (section II.B.1.a). This acid was converted to ethyl 3,5-dimethoxybenzoate, bp 102°C/0.2 mm (lit[34] bp 199-200°C/50 mm) in 88% yield by refluxing with ethanol containing 10% by volume of concentrated sulfuric acid. Lithium aluminum hydride reduction of the ester yielded 88% of theory of 3,5-dimethoxybenzyl alcohol. The alcohol was not purified further but was instead treated with thionyl chloride in refluxing diethyl ether to form 3,5-dimethoxybenzyl chloride, white solid, bp 101-102°C/0.55 mm, in 85% yield. This chloride was converted to the corresponding nitrile, 3,5-dimethoxybenzyl cyanide, bp 122-124°C/0.5-0.6 mm (93% yield), by refluxing with sodium cyanide in aqueous ethanol.

The last step in the sequence, the preparation of 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile, has been reported by Adams and coworkers[5]. Attempts to repeat their procedure led to the production of mixtures of di- and monomethylated nitriles. Two experiments were carried out. The first experiment, following closely the procedure outlined by Adams, resulted in a mixture composed of approximately 80% dimethylated nitrile together with 20%

monomethylated nitrile. It was not possible to separate these products by distillation. It was necessary to recycle the mixture in order to obtain pure dimethylated nitrile. A second experiment, exaggerating the reaction conditions described by Adams in order to favor the formation of the desired dimethylated nitrile, also led to an 80:20 mixture of nitriles as had the initial experiment, this in spite of the fact that a very large excess of methyl iodide had been used. The original work by Adams and coworkers was done before the VPC technique had been developed and it is felt that the product described by Adams was, in fact, a mixture of mono- and dimethylated nitriles, since the mixtures produced during the present investigation had properties identical to those described by Adams. Recycled nitrile mixtures led to the isolation of 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile of purity 97-99 area-% (VPC). A sample 99% pure boils at 130-133°C/0.6 mm, n_D^{20} 1.5223.

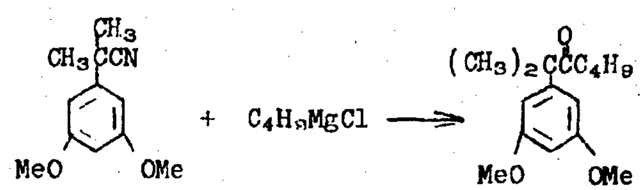
b. <u>2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile from Isobutyronitrile</u> Although the route to I by resorcylation of butanone was not practical, it was hoped that the substitution of a nitrile less susceptible to base-catalyzed self-condensation for the ketone would have better results and lead to this key intermediate.



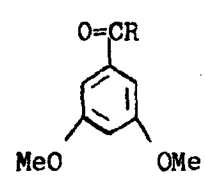
A single experiment was carried out. The results were similar to those in experiments where butanone had been used. Only a trace of what may have been the desired product could be detected. The major reaction product was 3,5-dimethoxyaniline, and a significant amount of 1-chloro-2,4-dimethoxybenzene was reclaimed unchanged.

This route to the nitrile intermediate has been abandoned in favor of the route from 3,5-dimethoxybenzoic acid, described above.

c. <u>2-(3,5-Dimethoxyphenyl)-2-methylheptanone-3, Precursor of VII</u> The reaction of pure 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile with butylmagnesium chloride was carried out on a 0.1-mole scale to yield 59% (by VPC) of the ketone (bp 120°C/0.65 mm, n_D^{20} 1.5114). The procedure was essentially that used by Adams and co-workers[5] for similar compounds. 2-(3,5-Dimethoxyphenyl)-2-methylheptanone-3 is a new compound.

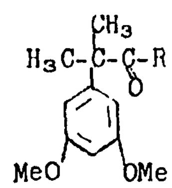


d. <u>Attempted Preparation of 2-(3,5-Dimethoxyphenyl)-2-methylheptane, Precursor of VII</u> Suter and Weston[85] and Adams and co-workers[4] have reported successful Wolff-Kishner reductions of 3,5-dimethoxybenzoylalkanes



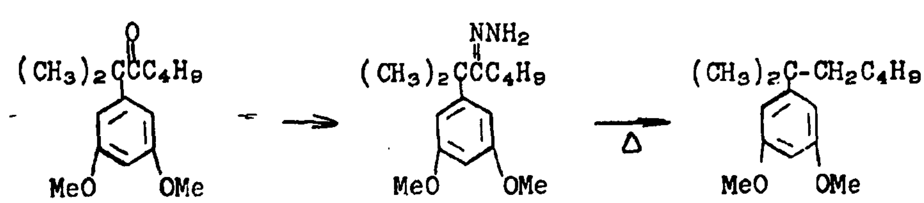
where R is a normal alkyl group of C_2 to C_8, in yields of from 54-85%. Since the work of both groups was published before 1946, the modern Huang-Minlon[46] modification of the Wolff-Kishner reaction was not used. Suter and Weston described their procedure, while Adams' group did not report the details of the reductions.

For ketones more nearly resembling 2-(3,5-dimethoxyphenyl)-2-methylheptanone-3, Adams and coworkers did not use the Wolff-Kishner reduction. For ketones of the type

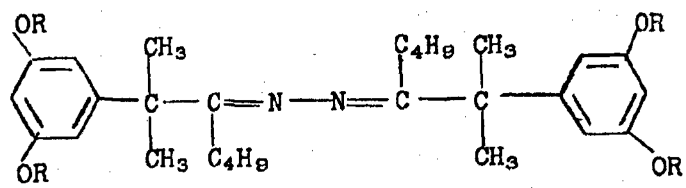


where R is a normal alkyl group, they reduced the ketone to the corresponding secondary alcohols, which were subjected to the Chugaev reaction and the resulting olefins hydrogenated.

In an effort to conserve time, we decided to attempt a Wolff-Kishner reduction of the 2-(3,5-dimethoxyphenyl)-2-methylheptanone-3, rather than follow the more complicated reduction scheme used by Adams and co-workers.



This type of ketone is sterically hindered, so the Wolff-Kishner procedure developed especially for sterically-hindered carbonyl functions by Barton, Ives, and Thomas[14] was selected. This procedure incorporates the Huang-Minlon technique, and also involves the use of anhydrous hydrazine. The results were negative, so it may be that this type of ketone does not respond to the Wolff-Kishner reduction. Instrumental evaluation revealed the major reaction product to be 2-(3,5-dihydroxyphenyl)-3-heptanone. Apparently a base-catalyzed ether cleavage had taken place, while the carbonyl function had remained intact. The yield of what apparently was 2-(3,5-dihydroxyphenyl)-3-heptanone, determined by VPC, was 29%. This material was collected as an amber, viscous liquid, bp 138-141°C/0.40 mm, n_D^{20} 1.5252. In addition to this reaction product, a trace of unaltered starting material was recovered, together with small amounts of lower-boiling unidentified materials. The reaction also produced a moderate quantity of brittle orange solid that was insoluble in water, ether, and benzene. It is possible that this solid may have been the ketazine, a known by-product of the Wolff-Kishner reduction[85].



R = CH_3 or H

The carbonyl reduction method used by Adams and co-workers for this type of ketone may be preferable to the Wolff-Kishner reduction. Sufficient good purity 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile was available to prepare more of the required ketone, but further work on this intermediate was suspended because of depletion of available funds.

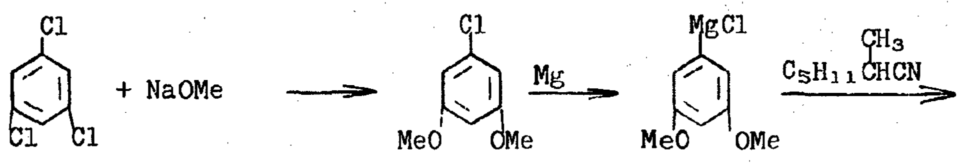
III. CONCLUSIONS

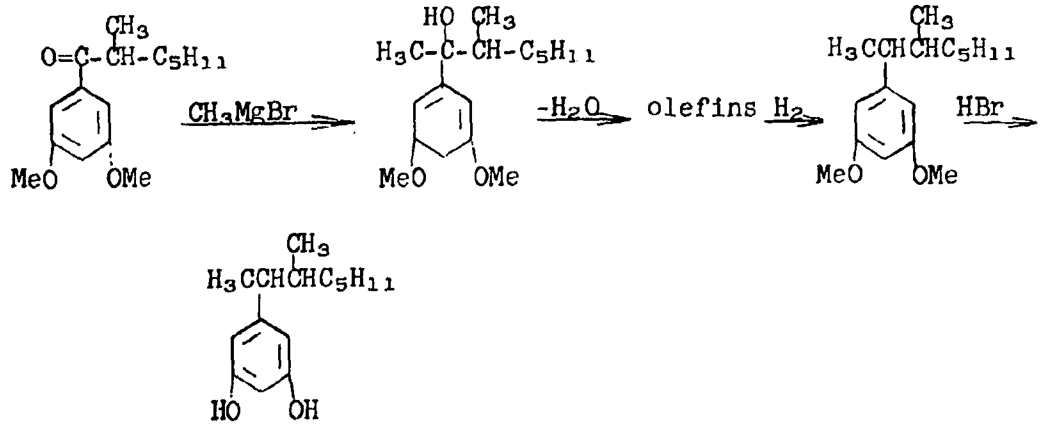
A. THE BEST COMMERCIAL SCALE PREPARATION OF 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE (I)

The key intermediates in this preparation are 1-chloro-3,5-dimethoxybenzene, its Grignard reagent, and 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2. The best preparation of the first of these is by the methanolysis of trichlorobenzene. The Grignard reagent is best prepared in tetrahydrofuran solution. The key carbinol could be formed by reaction of either 3-methyloctanone-2 or 2-methylheptanonitrile with the Grignard reagent. No really satisfactory preparation of 3-methyloctanone-2 is available. If there were one, there would still be the problem of the aldol self-condensation of the ketone during the Grignard reaction step. The reaction via 2-methylheptanonitrile meets the problem in a reasonably economical way.

The carbinol, 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2, is converted to 2-(3,5-dimethoxyphenyl)-3-methyloctane by dehydration and reduction. A catalytic hydrogenolysis might be suitable for this transformation. However, up to now, catalyst poisoning has been the main problem in all of the hydrogenation work.

2-(3,5-Dimethoxyphenyl)-3-methyloctane is cleaved to the desired resorcinol I by the known procedure.





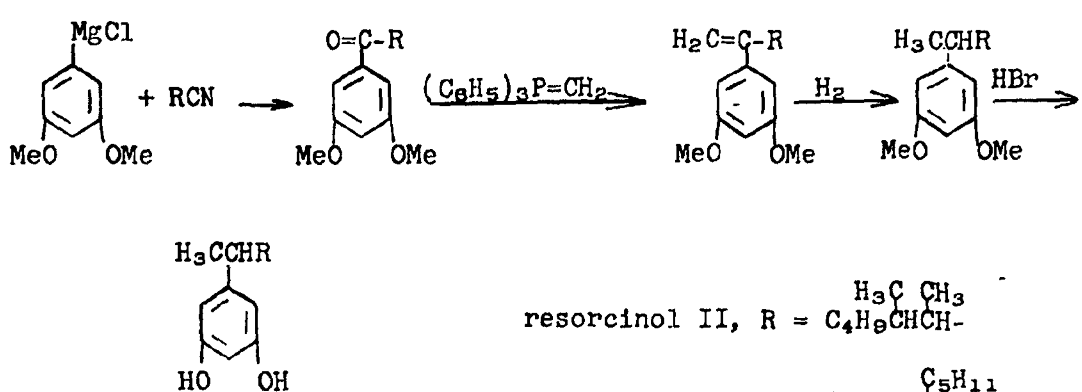
I

No practical way was found to circumvent a Grignard reaction involving 3,5-dimethoxyphenylmagnesium chloride. None of the other routes were close to being competitive.

B. LABORATORY PREPARATIONS OF SIX OTHER RESORCINOLS

1. Resorcinols II and IV

These two resorcinols were prepared in the laboratory by the reaction of the appropriate dimethylheptanonitrile with 3,5-dimethoxyphenylmagnesium chloride, followed by a Wittig reaction, reduction, and cleavage.

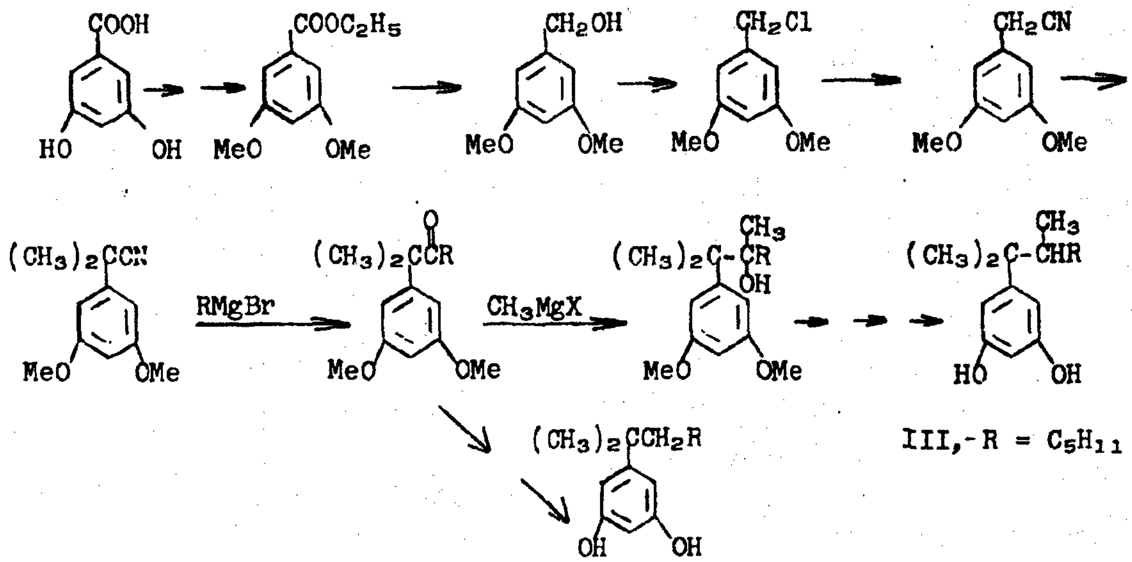


resorcinol II, R = $C_4H_9CH(CH_3)CH(CH_3)-$

resorcinol IV, R = $(CH_3)_2C(C_5H_{11})-$

2. Resorcinols III, VI, and VII

The recommended routes to these three resorcinols is by reaction of 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile with an alkyl Grignard followed by a subsequent Grignard reaction to give a precursor of III, or reduction to give precursors of VI or VII.



III, -R = C_5H_{11}

VI, R = C_3H_7
VII, R = C_4H_9

The preparation of resorcinol VII was actually carried as far as 2-(3,5-dimethoxyphenyl)-2-methylheptanone-3, and an unsuccessful attempt was made to reduce that intermediate directly to 2-(3,5-dimethoxyphenyl)-2-methylheptane.

3. Resorcinol V

No practical laboratory synthesis of resorcinol V was worked out.

IV. EXPERIMENTAL

A. COMPOUNDS AND REACTIONS RELATED TO 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE (I)

Because of the very large number of compounds examined on overlapping routes to this resorcinol, the compounds in the experimental section that relate to resorcinol I are arranged in an alphabetical, rather than logical, order.

1. 5-Aminoresorcinol

In response to our inquiry about 5-aminoresorcinol, the Dow Chemical Company stated that they had worked out a process for making this compound, but that the expected cost would be relatively high. Since they could not supply us with any research samples, they could not expedite the research program. It is questionable whether the existence of their process would provide the Chemical Corps with a source of large quantities more cheaply than would the benzyne reaction on 1-chloro-2,4-dimethoxybenzene.

2. Amyl Chlorosulfonate[13]

The reaction was carried out in a three-necked 500 ml flask equipped with stirrer, condenser, dropping funnel, and an inlet for dry nitrogen. The flask was charged with freshly distilled sulfuryl chloride (135 g, 1.0 mole). An ice-water bath was placed around the flask. Freshly distilled _n_-amyl alcohol (88.2 g, 1.0 mole) was added dropwise over a 45-minute period. Hydrogen chloride was evolved during the addition. The ice-water bath was removed and the mixture stirred for 1.5 hours, during which time dry nitrogen was bubbled through the reaction mixture to displace residual hydrogen chloride. The crude, sweet-smelling

chlorosulfonate was then transferred to a dropping funnel attached to the flask in which crude diamyl sulfite had been simultaneously prepared.

3. Bis(3,5-dimethoxyphenyl)amine

(See under 3,5-dimethoxyaniline, section IV.A.20.a.)

4. 1-Bromo-2,4-dimethoxybenzene

The reaction was carried out under a dry nitrogen atmosphere in a 3-necked, 2-liter flask equipped with dropping funnel, stirrer, condenser, and thermometer. Sodium hydroxide (100 g, 2.50 moles) was dissolved in 640 ml of water. 4-Bromoresorcinol (Aldrich) (94.5 g, 0.50 mole) was added, followed by the dropwise addition of dimethyl sulfate (224.5 g, 1.78 moles). The addition of the dimethyl sulfate required 45 minutes, the temperature of the mixture rising to 64°C at the completion of the addition. The mixture was then refluxed for 4 hours at 98°C. The reaction mixture was then transferred to a separatory funnel and extracted thrice with 250-ml portions of ether. The extracts were combined and washed twice with 200-ml portions of water, then dried over anhydrous magnesium sulfate. Ether was removed from the dried extract to leave 83.2 g of a brown, syrupy residue. This residue was distilled through a 1-foot glass helix-packed column to yield 76 g of 1-bromo-2,4-dimethoxybenzene (71% yield); bp 113-115°C/2.6 mm; n_D^{20} 1.5726; reported[73] bp 135°C/18 mm, 158-159°C/30 mm.

5. 2-Bromoheptane

a. From 1-Heptene The procedure followed was essentially that of

Spiegler and Tinker(83). Into a mixture of 294 g (2.994 moles) of 1-heptene and 750 g of chloroform, cooled to -20°C and stirred continuously, was introduced a rapid stream of dry hydrogen bromide. This reaction was carried out in subdued light and under a dry nitrogen atmosphere. The theoretical amount of hydrogen bromide was absorbed in about 12 hours. The reaction mass was then washed with cold water, and the oil was distilled through a short, packed column. After removal of the chloroform, 437.3 g of a mixture of 1- and 2-bromoheptane (82% of theoretical) was obtained. This mixture of bromides contained 22% of the desired 2-bromoheptane and 78% of 1-bromoheptane.

b. <u>From 2-Heptanol</u> Into a 1000 ml flask was placed 228 g (1.97 moles) of 2-heptanol and the solution was cooled to -20°C. To this cold stirred solution 194 g (0.72 mole) of phosphorus tribromide was added dropwise over 2 1/2 hours so that the reaction temperature was maintained below -10°C. The solution was then allowed to come to room temperature and stand overnight. The mixture was poured onto 400 g of ice and the organic layer was separated. After being washed with $NaHCO_3$ solution, it was distilled yielding 307 g (88%) of a colorless liquid, bp 64-66°C/25 mm.

6. <u>1-Chloro-2,4-dimethoxybenzene</u>

To a cold solution of 900 g (22.5 moles) of sodium hydroxide in 5400 ml of water was added 636 g (4.4 moles) of 4-chlororesorcinol. This solution was vigorously stirred and cooled to 10°C. An atmosphere of nitrogen was introduced, and from a dropping funnel 1990 g (15.75 moles) of dimethylsulfate was slowly added. This moderately exothermic addition required about 3.5 hours. At the end

of the addition the temperature of the mixture had risen to 53°C. The mixture was then refluxed for 17.5 hours. The reaction mass was extracted thoroughly with ether, the extract washed with water and dried over anhydrous magnesium sulfate. The ether was then removed under reduced pressure by means of a rotary evaporator. The residue was distilled through a short, packed column, and yielded 616.7 g (81%) of a pale yellow, almost colorless liquid: bp 77-80°C/0.65 mm, n_D^{20} 1.5478; reported: bp 135-7°C/17-18 mm [9].

<u>Anal</u>. Calcd. for $C_8H_9O_2Cl$: C, 55.7; H, 5.3; Cl, 20.5. Found: C, 55.5; H, 5.1; Cl, 20.4. The product has a tendency to darken on storage, so it should be stored under dry nitrogen in the cold and away from light.

7. <u>1-Chloro-3,5-dimethoxybenzene</u>

a. <u>From 3,5-Dimethoxyaniline</u> The diazonium solution was prepared[2] from 61.3 g (0.40 mole) of 3,5-dimethoxyaniline. This was subsequently reacted with freshly-prepared cuprous chloride solution (representing 0.50 mole CuCl). The reaction mixture was steam distilled. The organic portion of the steam distillate was taken up in ether. The ether extract was dried, then evaporated under reduced pressure leaving 33.6 g of an amber oil. This oil was then distilled under reduced pressure. The product was collected as a water-white liquid, bp 69-70°C/0.75 mm. After a brief period the distillate crystallized as small, colorless plates, mp 34-35.5°C (lit[33,42]: 38°C). The yield, based on VPC assay, was 29 g or 42%.

<u>Anal</u>. Calcd. for $C_8H_9ClO_2$: C, 55.7; H, 5.3; Cl, 20.5. Found: C, 55.6; H, 5.0; Cl, 20.6.

b. From Nitrosophenol The procedure of Goldschmidt and Suchanek(33) was followed. Anhydrous hydrogen chloride was passed into a flask containing a solution of 98.5 g (0.80 mole) of technical p-nitrosophenol in a mixture of 500 ml of absolute methanol and 500 ml of anhydrous diethyl ether. The gas was introduced at a rapid rate while maintaining the temperature at 28-33°C until vapors could be observed coming through the condenser and then for 1.3 hours longer. The mixture was then stirred in an ice bath for one hour and filtered. The precipitate was washed with ether and was then subjected to vacuum to remove residual solvent and hydrogen chloride.

The deamination procedure employed was that of Adams and Kornblum(3). A solution of 110 ml of concentrated hydrochloric acid in 1 liter of water was heated to 85°C, and then the previously collected amine hydrochloride was dissolved in it. The solution was cooled and at 15°C another 110 ml portion of concentrated hydrochloric acid was added. To this there was added portionwise a solution of 55.2 g (0.8 mole) of sodium nitrite in 120 ml of water while maintaining the temperature at 5-15°C. The resulting diazonium salt solution was stirred in an ice bath for 0.7 hour and then filtered. The deep red filtrate was immediately poured into 820 ml of cold 30-32% hypophosphorus acid and the resulting mixture allowed to stand overnight at room temperature.

The product was removed from the aqueous reaction medium by ether extraction. The ether extracts were combined, washed with several portions of 20% sodium hydroxide solution, and dried over anhydrous potassium carbonate. After filtration and removal of the

solvent, there was obtained 59.1 g of crude product (96% pure by VPC) representing a conversion of 41%. Distillation gave 51.3 g (37% conversion) of pure 1-chloro-3,5-dimethoxybenzene, bp 63-65°C/ 0.33 mm, which crystallized on standing, mp 38°C, reported[33,42] mp 38°C.

c. From 1,3,5-Trichlorobenzene

(1) Normal Quantity of Solvent A 2000-ml reaction flask was charged with 294.3 g (1.622 mole) of 1,3,5-trichlorobenzene (TCB) and 184 g (3.41 moles) of sodium methoxide in 500 ml of dry diglyme and the mixture was heated at reflux (164°C) for 42 hours.

After cooling to room temperature, the mixture was filtered and most of the solvent was removed by distillation at ambient pressure. Distillation of the residue gave the cuts listed in Table 6:

Table 6

RESULTS OF DISTILLATION.
SYNTHESIS OF 1-CHLORO-3,5-DIMETHOXYBENZENE

	Fraction		
	2	3	4
bp, °C/5 mm	92-96	96-97.1	97.5-99
Weight, g	38.3	35.7	147.7
Composition in area-%, by VPC			
diglyme	10.4	6.1	2.1
1-methoxy-3,5-dichlorobenzene	29.8	16.4	2.5
1-chloro-3,5-dimethoxybenzene (desired product)	59.8	77.8	94.7

The distillation was carried out using a 12-inch, glass helix-packed column. A more efficient fractionating system could easily effect better separation. The important point is that the over-all yield of 1-chloro-3,5-dimethoxybenzene based on VPC was 70%.

(2) With Insufficient Solvent 1,3,5-TCB was methanolized by the procedure described above, using 45.4 g (0.25 mole) 1,3,5-TCB; 29.7 g (0.55 mole) sodium methoxide; and 16.8 g (0.125 mole) diglyme. The weight of residue obtained was 41 g. Distillation gave three fractions: 2.1 g bp 41-85°C/4.3 mm, 23 area-% 3,5-dichloroanisole and 3 area-% 1-chloro-3,5-dimethoxybenzene; 10.1 g bp 85-89°C/4.3 mm, 73 area-% 3,5-dichloroanisole and 26 area-% 1-chloro-3,5-dimethoxybenzene; and 17.2 g bp 91-94°C/4.3 mm, 29.7 area-% 3,5-dichloroanisole and 70.3 area-% 1-chloro-3,5-dimethoxybenzene. Yields, by VPC, were 29% of 3,5-dichloroanisole and 34% 1-chloro-3,5-dimethoxybenzene.

(3) With More Nearly Optimum Quantity of Solvent The reaction was repeated as in the above paragraph, except that twice as much diglyme was used. The weight of residue obtained was 38.7 g. Distillation gave three fractions: 3.7 g bp 43-85°C/4.3 mm, 3 area-% 3,5-dichloroanisole and no 1-chloro-3,5-dimethoxybenzene; 3.7 g bp 85-91°C/4.3 mm, 60 area-% 3,5-dichloroanisole and 30 area-% 1-chloro-3,5-dimethoxybenzene; and 22.8 g bp 92-95°C/4.3 mm, 12.1 area-% 3,5 dichloroanisole and 87.7 area-% 1-chloro-3,5-dimethoxybenzene. The yield of 1-chloro-3,5-dimethoxybenzene was 50% (by VPC) and that of 3,5-dichloroanisole was 11% (by VPC).

d. Atempted Preparation of 1-Chloro-3,5-dimethoxybenzene from 1-Chloro-2,4-dimethoxybenzene, Lithium Chloride, and Dimethylformamide

A dry 1000-ml, three-necked flask was equipped with a Hershberg stirrer, dry nitrogen inlet, thermometer and Friedrichs condenser topped with a drying tube. The flask was charged with 1-chloro-2,4-dimethoxybenzene (43.2 g, 0.25 mole), lithium chloride (53.0 g, 1.25 moles) and 500 ml of dry N,N-dimethylformamide. Dry nitrogen was circulated through the system and stirring was begun. There was an immediate exotherm, the temperature rising to 52°C (probably due to the heat of solution of lithium chloride). The mixture was heated to 135°C for 3 hours. About half way through the heating period the solution developed an intense pink color. The reaction mixture was cooled to room temperature, transferred to a separatory funnel, and thoroughly shaken with water and ether. The ether extract was washed with water and dried over sodium sulfate. Ether was removed under reduced pressure, and the residue fractionated. Starting material, 1-chloro-2,4-dimethoxybenzene, was recovered almost quantitatively.

8. 4-Chloro-3-methoxytoluene

A 5000-ml reaction flask equipped with a stirrer, thermometer, and condenser was charged with 2800 ml of water and 291 g (7.26 moles) of sodium hydroxide were dissolved therein. After cooling to room temperature, 427.7 g (3.0 moles) of 4-chloro-m-cresol was added in portions. Then 651 g (5.16 moles) of dimethyl sulfate was added dropwise in 1.3 hours. The addition was started at 33°C and when it was completed, the temperature had risen to 55°C. The mixture was then heated at reflux for 17.5 hours. After cooling to room temperature, the reaction mixture was extracted with several 250-ml portions of ether. These

extracts were combined, washed with three 300-ml portions of water, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, distillation gave 435 g (93% yield) of 4-chloro-3-methoxytoluene, bp 87-88°C/6.5 mm; calculated for C_8H_9ClO: C, 61.5; H, 5.8; Cl, 22.6; found: C, 61.3; H, 5.8; Cl, 22.6. VPC showed the product to be greater than 99 area-% pure.

9. Attempted Formation of 5-Chlororesorcinol

A 500-ml flask equipped with a stirrer, thermometer, condenser with drying tube, and solids addition funnel was charged with 31.6 g (0.25 mole) of phloroglucinol in 100 ml of dry benzene. To this, 52.1 g (0.25 mole) of phosphorus pentachloride was added portionwise with no appreciable indication of reaction. The mixture was heated at reflux for 16 hours and, although a slow evolution of hydrogen chloride was evident throughout reflux, no definable product was obtained on work-up.

10. Diamyl Sulfate

a. Unsuccessful Attempt The Organic Syntheses procedure[84] for dibutyl sulfate (section IV.A.11, below) was used as a model for diamyl sulfate, without success. In this route, amyl chlorosulfonate, $C_5H_{11}OSO_2Cl$, is formed from diamyl sulfite and thionyl chloride. The route requires a distillation at a high pot temperature and resulted in formation of a large quantity of tar.

b. From Amyl Chlorosulfonate and Diamyl Sulfite[13] Crude diamyl sulfite was rapidly heated to about 115°C, and crude chlorosulfonate added dropwise over a 2-hour period. The temperature of the reaction mixture was not allowed to exceed 120°C during the addition. The mixture

was then heated an additional 30 minutes (temperature of the mixture not allowed to exceed 130°C), during which time dry nitrogen was bubbled through the mixture to displace residual gases. The reaction mixture was cooled to room temperature and 200 ml each of water and ether, together with a little charcoal were added. The mixture was then filtered through a "Celite" mat, and the filtrate transferred to a separatory funnel. The organic layer was set aside, and the aqueous layer extracted with additional ether. All organic phases were combined and washed with cold sodium carbonate solution, and finally with cold water. After drying over anhydrous magnesium sulfate, ether was removed under reduced pressure. The residue was distilled to yield 203 g (85%) of diamyl sulfate, bp 102-105°C/0.6 mm, n_D^{20} 1.4290; lit.[13,53] bp 117°C/2.5 mm, 128-130°C/3 mm, n_D^{20} 1.429.

11. Diamyl Sulfite[13]

The reaction was carried out in a three-necked 1000 ml flask equipped with stirrer, condenser, dropping funnel, and an inlet for dry nitrogen. The flask was charged with freshly distilled *n*-amyl alcohol (194 g, 2.2 moles). Freshly distilled thionyl chloride (130.9 g, 1.1 moles) was added dropwise over a 40-minute period. Hydrogen chloride was evolved during the moderately exothermic addition. The mixture was gently heated in an oil bath for 80 min. During this heating period dry nitrogen was bubbled through the reaction mixture to displace residual hydrogen chloride. The maximum temperature of the mixture during this preliminary heating period was 80°C.

12. Dibutyl Sulfate[84]

A 500-ml reaction flask was charged with 207.4 g (1.065 mole) of dibutyl sulfite. Then 72 g (0.533 mole) of sulfuryl chloride was added dropwise over a 20-minute period, the temperature rising from 25 to 36°C. The mixture was then heated at reflux for 0.5 hours. After this time, a distillation head was put on the flask and butyl chloride was distilled off to a pot temperature of 148°C. After cooling to room temperature, 50 ml of saturated sodium carbonate solution was added and, after stirring for 10 minutes, the mixture was allowed to stand one hour. The two layers were then separated and the upper layer was dried over calcium chloride. After filtration, distillation gave 93 g (83% yield) of dibutyl sulfate, bp 84-87°C/0.3-0.4 mm.

13. Dibutyl Sulfite[84]

A 1000-ml reaction flask was charged with 204 g (2.75 mole) of anhydrous *n*-butyl alcohol. Then 168.9 g (1.25 mole) of thionyl chloride was added dropwise in one hour. The temperature was kept at 35-45°C with a cooling bath during the first part of the addition, but as the evolution of hydrogen chloride became vigorous, heating was required to maintain this temperature. When addition was completed, the mixture was heated at reflux (pot temperature 193°C) for thirty minutes. Distillation then gave 230.2 g (95% yield) of dibutyl sulfite, bp 109-110°C/15 mm.

14. 4,4-Dichlorobuten-3-one-2[38]

A 1000-ml reaction flask was charged with 235.5 g (3.0 moles) of acetyl chloride. Then 233.3 g (1.0 mole) of anhydrous aluminum chloride

was added in portions while keeping the temperature below 10°C. The mixture, which was thick and difficult to stir, was then allowed to warm up to room temperature and 148 g (1.5 moles) of vinylidene chloride (Dow) was added dropwise over a period of 1.7 hours keeping the temperature below 30°C. The mixture was stirred for 30 minutes and was then hydrolyzed by pouring onto 2 liters of crushed ice. After stirring, the resulting layers were separated and the aqueous layer was extracted with three 300-ml portions of ether and discarded. The ethereal solutions and the organic layers were combined, washed successively with 500 ml of water, six 300-ml portions of 15% potassium carbonate, and two 500-ml portions of water and then dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was dark and fumed, indicating incomplete dehydrohalogenation of the intermediate β,β,β-trichloroketone, so the entire washing procedure was repeated. After drying and removal of the solvent, distillation of the residue gave 164.1 g (80% yield) of 4,4-dichlorobuten-3-one-2, bp 81°C/50 mm, n_D^{20} 1.4930; reported[38]: bp 58°C/15 mm, n_D^{20}1.4940; calculated Cl: 51.1%; found Cl: 50.8%.

15. Reaction of 4,4-Dichlorobuten-3-one-2 and Sodium Dimethyl Malonate

A 500-ml flask was charged with 38.9 g (0.28 mole) of 4,4-dichlorobuten-3-one-2. A solution of 0.25 mole of sodium dimethyl malonate in 125 ml of absolute methanol was added dropwise in 40 minutes while maintaining the temperature below 35°C. The first few drops of malonate salt caused reddish coloration, and by the end of addition the reaction mixture was deep red. The mixture was stirred at room temperature for

20 minutes, and then a solution of 29 g (0.5 mole) of potassium hydroxide in methanol was added, keeping the temperature below 35°C. The color was somewhat lighter, and a precipitate had formed. After filtration, the solvent was removed from the filtrate by warming under water pump vacuum and a dark solid residue was obtained. This was suspended in ether and 15% hydrochloric acid was added slowly until the solid dissolved. The ethereal portion was separated, washed with water, and dried over magnesium sulfate. After filtration and removal of the solvent, 45.3 g of dark red residue was obtained. Distillation failed to yield any distillate up to a pot temperature of 150°C/ 3.0 mm, and a rapid increase in pressure indicated extensive decomposition.

16. Diethyl Benzylphosphonate

A 500-ml flask was charged with 191.1 g (1.15 mole) of redistilled triethyl phosphite and 126.6 g (1.0 mole) of benzyl chloride. Heating was initiated and at a pot temperature of 145°C reaction started as evidenced by the condensation of the by-product, ethyl chloride, in a Dry Ice trap connected to the exhaust end of the reflux condenser. The mixture was heated at 150-155°C for 17 hours. At the end of this time the Dry Ice trap contained 54.5 g (85% of theory) of ethyl chloride. Distillation of the residue resulted in the isolation of 221.1 g of diethyl benzylphosphonate, bp 100°C/0.3 mm, n_D^{20} 1.4966, greater than 99 area-% pure by VPC. The yield was 97% of theory.

17. Diethyl 1-Phenylamylphosphonate

A 500-ml reaction flask was charged with 9.4 g of 51.8% of sodium hydride (0.2 mole), 42.1 g (0.2 mole) of dibutyl sulfate, and 45.6 g (0.2 mole) of diethyl benzylphosphonate in 100 ml of anhydrous

1,2-dimethoxyethane. Heating was initiated. At 75°C evolution of hydrogen was very vigorous and the reaction was self-sustaining. The temperature rose to 90°C with vigorous reflux before subsiding. The mixture was then heated at reflux for one hour. After cooling, the mixture was filtered and the solvent removed by distillation at ambient pressure. Distillation of the residue gave 46.3 g (82% yield) of diethyl 1-phenylamylphosphonate, bp 118-120°C/0.3 mm, n_D^{20} 1.4868, greater than 99 area-% pure by VPC.

18. Diethyl 1-Phenylethylphosphonate

a. By the Arbuzov Reaction A 500-ml reaction flask was charged with 83.1 g (0.5 mole) of triethyl phosphite and 56 g (0.315 mole) of 1-phenylethyl bromide. Heating was initiated and the mixture was heated at 155-177°C for 1.35 hours. The by-product, ethyl bromide, was removed as formed. A total of 30.2 g of distillate was obtained, which was 91% of theory for ethyl bromide. Distillation of the pot residue gave 50 g (68% yield) of diethyl 1-phenylethylphosphonate, bp 101-102°C/0.22 mm, n_D^{20} 1.4938, greater than 99 area-% pure by VPC.

b. By the Methylation of Diethyl Benzylphosphonate A 1000-ml reaction flask was charged with 113.1 g (0.495 mole) of diethyl benzylphosphonate, 67 g (0.53 mole) of freshly distilled dimethyl sulfate, and 23.0 g of 51.8% sodium hydride dispersion (contains 0.495 mole of NaH) in 200 ml of anhydrous 1,2-dimethoxyethane. Heating was initiated. At a pot temperature of 60°C hydrogen evolution started. The temperature was kept between 83 and 91°C until hydrogen evolution was complete. The mixture was then heated at

reflux for 75 minutes. After cooling, the mixture was filtered and the solvent removed at reduced pressure. Distillation gave 108.2 g of a fraction, bp 113-114°C/0.5 mm, n_D^{20} 1.4944, which VPC showed to be 27 area-% diethyl 1-phenylethylphosphonate and 73 area-% diethyl benzylphosphonate.

19. <u>2-(3,5-Dihydroxyphenyl)-3-methyloctane (I)</u>

2-(3,5-Dimethoxyphenyl)-3-methyloctane (20.0 g, 0.076 mole), 48% hydrobromic acid (65 ml) and glacial acetic acid (200 ml) were combined in a three-necked, 1-liter flask equipped with condenser, stirrer, and thermometer. The mixture was stirred and refluxed for six hours. After cooling, the mixture was poured onto 300 g of cracked ice and 300 ml of water. Solid sodium bicarbonate was cautiously added to neutralize the strongly acidic mixture. This was followed by ether extraction. The ether extract, extract I, was then extracted with 10% aqueous sodium hydroxide. The basic extract was acidified with hydrochloric acid and extracted with ether, extract II. Extract I was evaporated to yield 2.5 g of what was presumably uncleaved ether. Extract II was evaporated to yield 27.6 g of a brown-amber liquid which was distilled to yield 14.0 g of 2-(3,5-dihydroxyphenyl)-3-methyloctane, bp 154°C/0.23 mm. The yield of cleaved product was 90% (98.5 area-% pure by VPC), with a conversion of 78%. Its VPC is shown in Figure 3. It was determined on an Aerograph Model A-350, 6-ft, 15% Apiezon L on 35-80 mesh Chromosorb W, 275°C, 85 cc He/min. The VPC is compared with that of a sample from the Chemical Center, PL5386, which we had had for several months (and which might have become somewhat degraded), in Table 7. The two VPC's being compared in Table 7 were run on the same instrument under the same conditions, and in succession.

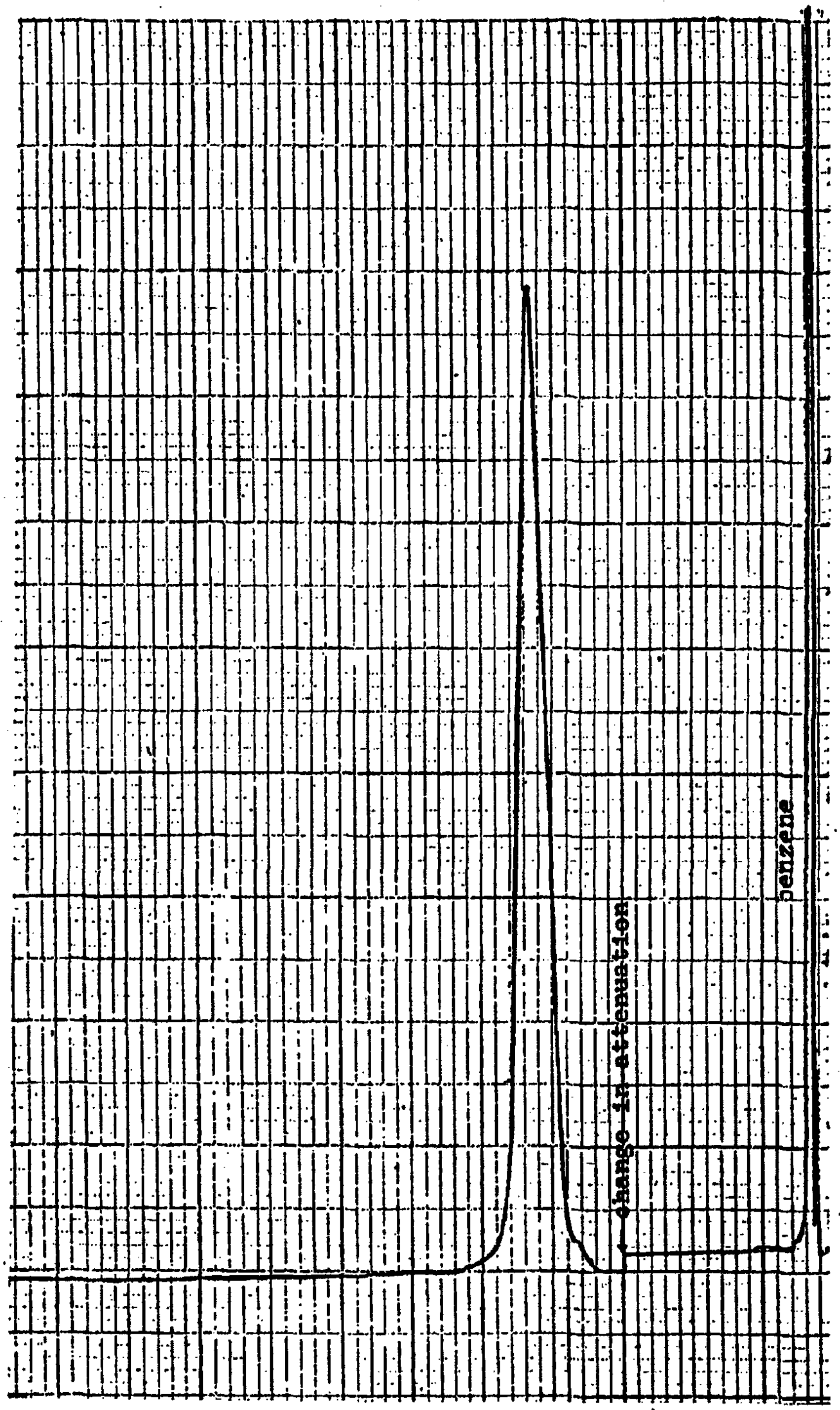


Figure 3. Vapor phase chromatogram of 2-(3,5-dihydroxyphenyl)-3-methyloctane.

Table 7

VPC'S OF 2-(3,5-DIHYDROXYPHENYL)-3-METHYLOCTANE

Sample MRC28883		Sample PL5386	
Retention time, min.	Area-%	Retention time, min.	Area-%
		3.0	1.3
3.7	1.5	3.5	15.8
4.3	98.5	4.3	70.0 product
		5.2	5.5
		5.8	7.3

The infrared spectrum of MRC28883, Figure 4, is the same as that of the 4.3 minute component of PL5386 after its separation by VPC.

Anal. Calculated: C, 76.2; H, 10.2; found: C, 76.3; H, 10.2.

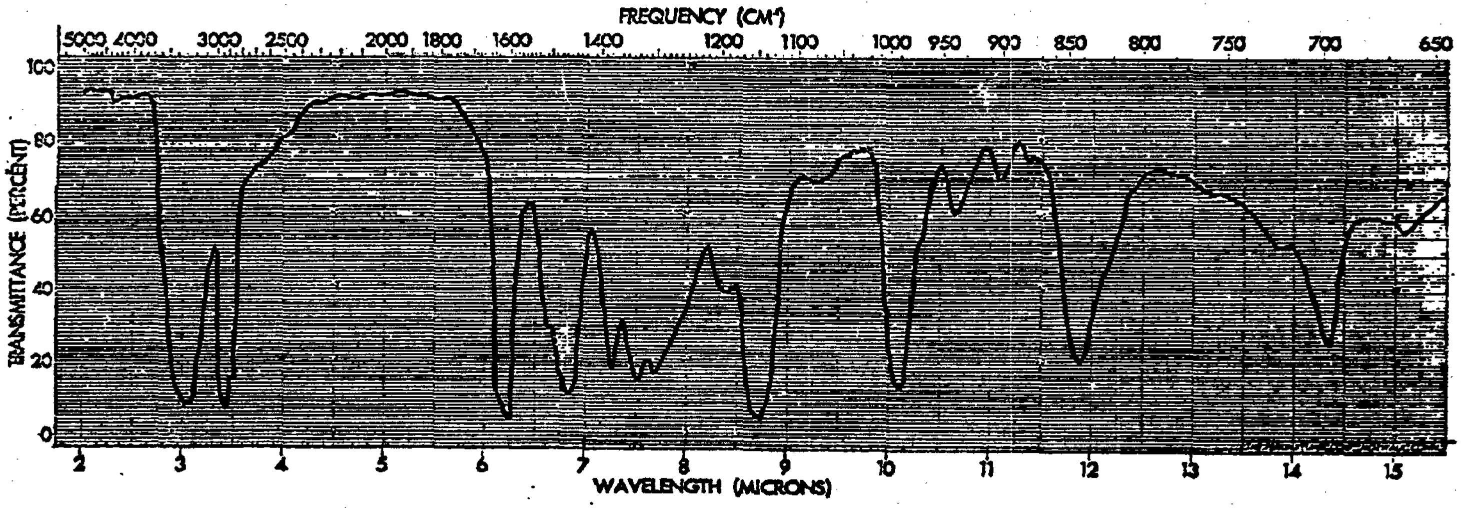


Figure 4. Infrared spectrum of 2-(3,5-dihydroxyphenyl)-3-methyloctane, Perkin-Elmer model 21 double beam spectrophotomer, liquid film, sodium chloride optics.

20. 3,5-Dimethoxyacetophenone

a. From 3,5-Dimethoxybenzonitrile The procedure of Baker and Smith(11) was followed. Into a 2-liter flask blanketed with nitrogen was placed 100 g (0.615 mole) of 3,5-dimethoxybenzonitrile (obtained from the Army Chemical Center) and 650 ml of anhydrous ether. To this stirred, heterogeneous solution was added rapidly 222 ml of a 3 M solution of methylmagnesium bromide in ether (Arapahoe Chemicals, Inc., Boulder, Colorado). The temperature was maintained at 30°C during the addition and the reaction mixture was allowed to stand 16 hours at room temperature. After heating under reflux for 4 hours, the mixture was decomposed by pouring it onto 2 kg of ice and 50 ml of concentrated sulfuric acid and stirring for 2 hours. The ether was separated, washed with bicarbonate solution and removed, leaving a dark brown residue. The residue was distilled under nitrogen, bp 107-109°C/0.45 mm, reported(57) 151-152°C/10 mm. The yield of 3,5-dimethoxyacetophenone was 71 g (64%).

b. From 3,5-Dimethoxybenzoyl Chloride The procedure of Cason and Prout(18) was followed. Into a 500-ml flask blanketed with nitrogen was placed 175 ml of a 3 M solution of methylmagnesium bromide (0.53 mole) in ether (Arapahoe Chemicals, Inc., Boulder, Colorado) and an additional 100 ml of anhydrous ether. The Grignard solution was cooled in an ice bath and 54 g (0.3 mole) of anhydrous cadmium chloride was added in portions so as to minimize foaming. The ice bath was removed and the heterogeneous solution was stirred for 15 minutes. The ether was then distilled rapidly by heating in an oil bath with stirring until a dark semi-solid residue remained. After addition of 150 ml

of dry thiophene-free benzene, the distillation was resumed until most of the benzene had been removed. After 100 ml of benzene had been added to the residue, the mixture was stirred and heated under reflux until the cake had been broken up and dispersed through the mixture. A solution of 52 g (0.26 mole) of dimethoxybenzoyl chloride in 100 ml of benzene was added during a 15-minute period. After the exothermic reaction had subsided, the mixture was heated under reflux for one hour with stirring.

The organometallic complex was decomposed with a mixture of 1000 g of ice and 50 ml of concentrated sulfuric acid. The water was separated and extracted twice with benzene. The combined benzene layers were washed with 5% sodium hydroxide solution. The benzene was then removed under reduced pressure and the red oil that remained was distilled under nitrogen, bp 167-172°C/21 mm. Thirty g (64%) of 3,5-dimethoxyacetophenone was obtained as a colorless, mobile liquid.

c. <u>From 3,5-Dimethoxybenzoic Acid and Methyllithium</u> The procedure was adapted from the work of Tegner[86]. A solution of methyllithium was prepared by the addition of 212.9 g (1.5 mole) of iodomethane in 125 ml of dry diethyl ether to 20.8 g (3.0 mole) of lithium ribbon that had been cut into small pieces suspended in 3000 ml of dry diethyl ether under nitrogen. A 25-ml portion was added to initiate the reaction and the remaining iodomethane solution was added at such a rate as to maintain reflux. When addition was completed, the mixture was refluxed for three hours and was then allowed to stand overnight.

To this solution there was then added 149.3 g (0.825 mole) of 3,5-dimethoxybenzoic acid. The acid was added in portions as a solid at a rate that maintained reflux. The mixture was heated at reflux for one hour and was then hydrolyzed by pouring onto 4 liters of crushed ice in one liter of water. After stirring for one hour, the ether layer was separated. The aqueous layer was extracted with several portions of ether and the ethereal solutions were combined and dried over anhydrous magnesium sulfate.

The aqueous layer was neutralized with concentrated hydrochloric acid to yield, after filtration and drying in vacuo, 43.8 g (0.25 mole) of unreacted 3,5-dimethoxybenzoic acid.

The ether solution was filtered and the solvent removed under reduced pressure. Distillation gave three fractions, (1) bp 81-83°C/0.3 mm, (2) bp 83-98°C/0.3 mm, and (3) bp 99-100°C/0.3 mm. Fraction (1) was identified by its infrared spectrum and elemental analysis as 3,5-dimethoxy-α-methylstyrene. (Calculated for $C_{11}H_{14}O_2$: C, 74.2; H, 7.9. Found: C, 74.3; H, 7.8.) VPC indicated fraction (2) to be a mixture of 37% 3,5-dimethoxy- -methylstyrene and 63% 3,5-dimethoxyacetophenone. Fraction (3) was found to be 99.8% desired product. The yield of 3,5-dimethoxyacetophenone was 35% and of the by-product 3,5-dimethoxy-α-methylstyrene was 12%.

21. 3,5-Dimethoxyaniline

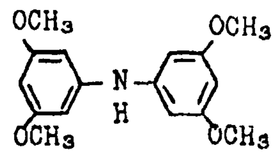
3,5-Dimethoxyaniline has been worked up and isolated in two different ways: crystallization and vacuum distillation. The latter is the more efficient method of isolation, resulting in a better yield.

a. <u>Isolated by Crystallization</u> The procedure is an example of the benzyne reaction[29].

Sodamide was prepared according to the directions of Vaughn, Vogt and Nieuwland[90] from 48.3 g (2.10 g-atoms) of sodium and 1.3 g of hydrated ferric nitrate in 2 liters of liquid ammonia. Then 177.8 g (1.03 moles) of 1-chloro-2,4-dimethoxybenzene was added over a period of about 30 minutes. The mixture was allowed to stir at reflux for 40 minutes. Excess sodamide was then destroyed by the addition of 119.3 g (2.23 moles) of solid ammonium chloride. This latter addition was exothermic and, as a result, required 1.25 hours to complete. The ammonia was then allowed to evaporate. The residual solid was extracted with 2 liters of ether. The amine was precipitated from the ether solution as its hydrochloride, which was subsequently treated in water with ammonium hydroxide. The viscous, brown oil (95 g) that resulted solidified after a brief period; it was recrystallized from ethanol to give 75 g of brownish-pink needles, mp 53-55°C. Vapor phase chromatography indicated the presence of a minor contaminant. This contaminant may be removed by subsequent recrystallization from ethanol. Pure 3,5-dimethoxyaniline melts at 56.5-58°C. The desired amine present, indicated by VPC, after the one recrystallization was about 71.1 g for a minimum yield of 45%. The infrared spectrum of product was consistent with a dimethoxyaniline. Its structure was confirmed by its acetanilide, mp 155.5-157°C; literature value for 3,5-dimethoxyacetanilide: 157°C[62,82].

Anal. Calcd. for $C_8H_{11}O_2N$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.7; H, 7.2; N, 9.1.

The minor contaminant, described above, was isolated in milligram quantities from the mother liquor. It was recrystallized from ethanol giving tiny, white, felted needles, mp 140-41°C. Its infrared spectrum was consistent with the proposed structure:



b. Isolated by Vacuum Distillation Sodamide was prepared from 56.4 g (2.45 g-atoms) of sodium and 1.5 g of hydrated ferric nitrate in 2.7 liters of liquid ammonia. Then 207 g (1.2 moles) of 1-chloro-2,4-dimethoxybenzene was added dropwise over 1.5 hour period. The mixture was allowed to stir at reflux for 25 minutes. Excess sodamide was then destroyed by the portionwise addition of 139.5 g (2.61 moles) of solid ammonium chloride. The ammonia was then allowed to evaporate. The residual solid was stirred with 1500 ml of ether for 1 hour. The ethereal slurry was filtered, and the collected solid was washed with an additional 500 ml of ether. The ether extracts were combined and washed with 500 ml of water, then dried over magnesium sulfate. The ether was removed under reduced pressure leaving an amber, viscous residue which weighed 183.5 g. This residue was distilled, and 3,5-dimethoxyaniline (119.9 g for a 65% yield) was collected at 112°C/0.67 mm, mp (uncorr) 54.5 - 55.5°C; reported bp 115°C/0.5 mm[82], mp 46°C[78,82].

22. 3,5-Dimethoxybenzoic Acid

The procedure of Mauthner[58] was followed. To a cold solution of 200 g (5 moles) of sodium hydroxide in 1250 ml of water in a 5-liter flask blanketed with nitrogen was added 154 g (1 mole) of 3,5-dihydroxybenzoic acid. The flask was closed immediately and the mixture was stirred until all of the acid had dissolved. Then 220 g (1.75 moles) of dimethyl sulfate was added and the solution stirred for 20 minutes, being cooled with cold water to maintain the temperature below 30 to 35°C. A second portion of 220 g of dimethyl sulfate was then added and during the next ten minutes the temperature was not allowed to rise above 40 to 45°C. The contents of the flask were then heated under reflux for two hours. In order to saponify the small amount of ester that was produced, a solution of 50 g of sodium hydroxide in 75 ml of water was added and the contents were heated under reflux for an additional two hours. The reaction mixture was cooled and acidified with dilute hydrochloric acid. The precipitated dimethoxybenzoic acid was collected by filtration and washed well with cold water. The wet product was boiled in three liters of water, cooled, filtered and dried. The yield (mp 179-82°C; reported[17] 182°C) was 160 g (88%).

23. 3,5-Dimethoxybenzoyl Chloride

The procedure of Munch-Petersen[59] was followed. Into a 250-ml flask blanketed with nitrogen was placed 55 g (0.3 mole) of 3,5-dimethoxybenzoic acid and 124 g (1.05 moles) of thionyl chloride. The mixture was stirred and heated under reflux for three hours. The thionyl chloride was removed under reduced pressure leaving a brown

residue that was distilled under nitrogen through a Claisen head yielding 52 g (87%) of a colorless liquid, dimethoxybenzoyl chloride, bp 158°C/20 mm; reported[56] 157°C/16 mm.

24. <u>2-(3,5-Dimethoxybenzoyl)heptane</u>

A 500-ml round-bottomed flask equipped with a stirrer, thermometer, condenser with drying tube, dropping funnel, and nitrogen inlet, was flamed out under nitrogen and charged with 7.3 g (0.3 g-atom) of magnesium turnings. A solution of 43.2 g (0.25 mole) of 1-chloro-3,5-dimethoxybenzene in 54.1 g (0.75 mole) of freshly distilled tetrahydrofuran was prepared and about 15 ml added to the magnesium. Ethyl bromide, 1 g, was then added and a vigorous reaction started. Heating was initiated and the remainder of the tetrahydrofuran solution added in 30 minutes. The mixture was heated to reflux (78-86°C) and maintained there for three hours.

After cooling the Grignard reagent to room temperature, a solution of 34 g (0.27 mole) of 2-methylheptanonitrile in 30 ml of dry tetrahydrofuran was added dropwise in 27 minutes. The addition was started at 27°C and the temperature had risen to 40°C by the end of the addition. The mixture was then heated to 60°C for six hours and allowed to stand over the weekend.

To the reaction mixture was added 160 g of a 40% sulfuric acid solution. The reaction was quite vigorous and an ice bath was employed to keep the temperature below 40°C. After stirring for 15 minutes, the solvent was removed by distillation at ambient pressure. Then 40 g of a 50% sulfuric acid solution was added and

the mixture heated for one hour at 95-100°C. After cooling a 50-ml portion of ether was added and the resulting two layers were separated. The aqueous layer was extracted with three 75-ml portions of ether. The ethereal solutions were combined, washed with three 100-ml portions of water, and dried over anhydrous magnesium sulfate.

After filtration and removal of the solvent, 68.4 g of dark, oily residue was obtained. Distillation gave:

Fraction No.	bp, °C/mm	Weight, g	n_D^{20}
1	up to 90/0.25	-	1.4589
2	120-132/0.2	1	1.5288
3	133-138/0.2	43	1.5116
4	142-148/0.2-0.5	1.5	1.5224

Fraction 3 represented a 71% yield of product of 94 area-% purity by VPC. Redistillation resulted in the isolation of 2-(3,5-dimethoxybenzoyl)heptane, bp 134°C/0.2 mm, n_D^{20} 1.5100, in greater than 96 area-% purity.

25. 3,5-Dimethoxy-N,N-dibutylaniline

(See under use of lithium alkyl amides for the resorcylation reaction, section IV.A.45.e.)

26. 3,5-Dimethoxyphenylmagnesium Chloride

a. Unsuccessful Attempts

(1) Solventless at Elevated Temperature A 50-ml three-necked flask was fitted with thermometer, air condenser topped with a drying tube, dry nitrogen inlet, and magnetic stirrer. Magnesium turnings (1.8 g, 0.075 g-atom) were placed into the flask together

with a small crystal of iodine. The entire reaction system was then flamed out and allowed to cool under a stream of dry nitrogen. When the system had cooled, 1-chloro-3,5-dimethoxybenzene (8.6 g, 0.05 mole) was rapidly added. The mixture was then stirred and heated at 150-160° for 4.5 hours. The mixture developed a slight gray color (probably due to the presence of finely divided magnesium). A small aliquot gave a negative Michler's ketone test[50]. The temperature of the mixture was increased to 190-200°C for an additional 13 hours. No Grignard reagent formed, and starting halide was recovered.

(2) With Zinc Sulfate Activator[69]: Zinc sulfate heptahydrate was dehydrated by heating in a sand bath under dry nitrogen until the bath temperature reached 280°. Most of the water of hydration was evolved at about 170°.

A dry, 500 ml, three-necked flask was equipped with mechanical stirrer, water-cooled condenser, dry nitrogen inlet and long-stemmed thermometer. Magnesium turnings (3.6 g, 0.15 g-atom), anhydrous zinc sulfate (33 mg) and 1-chloro-3,5-dimethoxybenzene (17.2 g, 0.10 mole) were placed into the flask and heated and stirred, under a slow stream of dry nitrogen at 135-45°C for about 0.75 hour. At this stage a dark color developed, probably due to finely divided magnesium. The mixture was heated over the same temperature range for an additional 1.25 hours. Freshly-distilled xylene (80 ml) and an additional 33 mg of anhydrous zinc sulfate were added. The vigorously-stirred, gray-black mixture was heated to reflux, 143°C, for 20 hours. A negative Michler's ketone test indicated the absence of Grignard reagent.

(3) <u>With Gilman-Kirby Activator</u>[31] A dry, 500 ml, three-necked flask was equipped with dry nitrogen inlet, stirrer, Claisen head topped with a pressure-equalizing dropping funnel, condenser set for distillation, and bent receiving adapter equipped with drying tube and receiver. All apparatus had been previously oven-dried. Magnesium turnings (5 g), iodine (2.5 g), and 100 ml of dry benzene were combined in the flask and stirred vigorously. A stream of dry nitrogen was circulated above the mixture throughout the preparation. The mixture was deep purple. Dropwise addition of 5 ml of anhydrous ether was carried out over a 20-minute period. The mixture changed from purple to brown to colorless during the course of the addition. Solvent was then removed by distillation using an oil bath. When all of the solvent had been removed, the temperature of the oil bath was increased to between 150°C and 160°C. The solid residue was heated over this temperature range for 10 minutes. The dull gray residue was then ready for use.

A 50 ml, three-necked flask was equipped with thermometer, air-cooled condenser topped with a drying tube, dry nitrogen inlet, and magnetic stirrer. Magnesium turnings (1.2 g, 0.05 g-atom) and the activator prepared as above (259 mg) were added to the flask. The entire reaction system was then flamed out and allowed to cool under a stream of dry nitrogen. When the system had cooled, still under a slow stream of dry nitrogen, 1-chloro-3,5-dimethoxybenzene (8.6 g, 0.05 mole) was rapidly added. The vigorously-stirred mixture was heated at 232°C for 28 hours. Initially the mixture turned milky, and finally turned dark brown. Most or all of the magnesium turnings had remained intact. An aliquot gave a negative Michler's ketone test. Starting halide was recovered.

(4) <u>With Magnesium Powder</u> A 50 ml, three-necked flask was equipped with thermometer, air condenser topped with a drying tube, dry nitrogen inlet, and magnetic stirrer. Magnesium powder (Matheson Coleman and Bell) (1.2 g, 0.05 g-atom) was placed in the flask, and the entire reaction system was flamed out and allowed to cool under a stream of dry nitrogen. When the system had cooled, still under a slow stream of dry nitrogen, 1-chloro-3,5-dimethoxybenzene (8.6 g, 0.05 mole) was rapidly added. The mixture was vigorously stirred and heated to reflux, 232°C, for 27.5 hours. An aliquot gave a negative Michler's ketone test.

(5) <u>Entrainment Method Using Ethylene Bromide</u>[64] A 500 ml, four-necked flask was equipped with a 125 ml pressure-equalizing dropping funnel, dry nitrogen inlet, stirrer, condenser topped with drying tube, and long-stemmed thermometer. Magnesium turnings (2.84 g, 0.116 g-atom) were placed in the flask, the entire system was flamed out and allowed to cool under a stream of dry nitrogen. 1-Chloro-3,5-dimethoxybenzene (8.6 g, 0.05 mole) dissolved in 50 ml of anhydrous ether was then added. The resultant mixture was stirred and heated to gentle reflux, under a slow stream of dry nitrogen. Ethylene bromide (9.3 g, 0.05 mole) dissolved in 50 ml of anhydrous ether was then added dropwise. An attempt was made to keep the rate of addition at about 1 drop/15 seconds as recommended by Pearson[64], but it was not possible to fabricate a Hershberg dropping funnel to give a slow enough dropping rate. As a result, the rate of addition varied greatly, but, in general, was slower than the recommended rate. The addition was interrupted after about 7 hours, and the reaction mixture, now dark black, was

allowed to stand overnight under dry nitrogen. The addition was continued and required an additional 5 hours to complete. Most of the magnesium turnings still seemed intact. A Michler's ketone test on a small aliquot of the reaction mixture appeared to be negative. However, the hydrolysis stage of the test was exothermic, and a white precipitate formed. Magnesium turnings, 1.6 g, were recovered. The residual reaction mixture was hydrolyzed with cracked ice and dilute hydrochloric acid. Ether extraction, followed by distillation yielded only starting halide.

(6) Using Ethylene Bromide and Magnesium Powder A dry 250-ml three-necked flask was equipped with dry nitrogen inlet, stirrer, condenser topped with drying tube, and a small pressure-equalizing dropping funnel. The flask was charged with magnesium powder (Matheson Coleman and Bell, 20 mesh) (1.5 g, 0.062 g-atom) and a small crystal of iodine. The system was flamed out and allowed to cool under a stream of dry nitrogen. The dropping funnel was charged with 1-chloro-3,5-dimethoxybenzene (10.7 g, 0.062 mole) dissolved in freshly distilled tetrahydrofuran (du Pont Co.; has negligible water content) (13.4 g, 0.186 mole). About 5 ml of this solution, together with a few drops of ethylene bromide, was added to the magnesium powder and stirring was begun. There was no sign of reaction initiation. The remaining halide solution was added dropwise over a period of 15 minutes. Heating was commenced midway during the halide-THF addition; the temperature of the mixture had reached 50°C by the end of this addition. The mixture was heated at reflux (68°C) for two hours. A negative Michler's ketone test, together with recovery of 1.5 g of magnesium indicated that none of the desired 3,5-dimethoxyphenylmagnesium chloride had formed.

(7) Using Tetrahydrofuran and N-Methylmorpholine as a Mixed Solvent System A dry 250-ml three-necked flask was equipped with a thermometer, condenser topped with a drying tube, pressure-equalizing dropping funnel, and dry nitrogen inlet. Magnesium shavings (Matheson Coleman and Bell) (3 g, 0.125 g-atom) and a small crystal of iodine were placed into the flask, and the entire system was flamed out and allowed to cool under a stream of dry nitrogen. The dropping funnel was charged with 1-chloro-3,5-dimethoxybenzene (21.4 g, 0.124 mole) dissolved in a mixed solvent system composed of tetrahydrofuran (24.1 g, 0.334 mole) and N-methylmorpholine (2.7 g, 0.027 mole). Both of these solvents had been freshly distilled prior to use. About 5 ml of this solution, followed by 0.5 ml of ethyl bromide, was run in with the magnesium, but no initiation was observed. A second 0.5-ml portion of ethyl bromide was added, also with no effect. Dropwise addition of the remaining halide solution was begun. The addition required 30 minutes. The solution was refluxed for an additional 4.5 hours, but there was no evidence of Grignard formation, the magnesium appearing unaffected. A Michler's ketone test was negative. Further heating at reflux the following day also resulted in a negative Michler's ketone test.

b. Successful Method: The Reactive Solvent Method with Tetrahydrofuran(71) A 500-ml, three-necked flask was equipped with thermometer, Friedrich's condenser topped with a drying tube, stirrer, 125-ml pressure-equalizing dropping funnel, and dry nitrogen inlet.

Magnesium shavings (Matheson Coleman and Bell) (6.0 g, 0.248 g-atom), and a small crystal of iodine were placed into the flask, and the entire system was flamed out and allowed to cool under a stream of dry nitrogen. The dropping funnel was charged with 1-chloro-3,5-dimethoxybenzene (42.8 g, 0.248 mole) dissolved in freshly-distilled tetrahydrofuran (supplied by the du Pont Company and having a negligible water content) (53.6 g, 0.744 mole). About 10 ml of this solution was run in with the magnesium. A few drops of ethyl bromide were added to initiate reaction. Stirring was begun, the iodine color discharged, and a very exothermic reaction set in. Dropwise addition of the remaining tetrahydrofuran-halide solution was started. The addition required about 1 hour, the temperature of the mixture finally reaching 75°C. The mixture, a dark yellow liquid together with a lot of as yet unreacted magnesium, was heated to vigorous reflux (79—85.5°C) for an additional two hours. When the temperature of the mixture reached 85.5°C, reflux from the condenser ceased. The reaction mixture now appared as a dark, brown-amber syrup; only a small amount of magnesium remained unreacted (about 0.5 g). A positive Michler's ketone test was obtained.

The yield was determined by titration. The reaction mixture was transferred to a 250-ml volumetric flask (the Grignard reagent hydrolyzes only slowly in air), and was diluted to the mark with tetrahydrofuran. Twenty-ml aliquots were pipetted into 50 ml of 0.5 N hydrochloric acid and 50 ml of water, heated in a hot water bath at 80-85°C for 30 minutes, and back-titrated with 0.4 N NaOH with phenolphthalein as indicator. The yield of Grignard reagent, thus determined, was 79%.

Proof that the desired Grignard reagent had actually been formed was obtained by hydrolysis of the remaining bulk of the Grignard solution. It was poured onto 500 g of cracked ice with vigorous stirring, and then was acidified by the addition of 55 ml of 6 N hydrochloric acid. The hydrolysate was extracted with two 150 ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure. The amber, oily residue was then distilled under reduced pressure, bp 77-78°C/4.6 mm, n_D^{20} 1.5254 (lit. for m-dimethoxybenzene:(76) bp 214-215°C/750.4 mm).

An authentic specimen of m-dimethoxybenzene (Eastman No. 314) was obtained n_D^{20} 1.5249. Its infrared spectrum was identical to that of the product obtained from the above hydrolysis procedure.

27. 2-(3,5-Dimethoxyphenyl)-3-methyloctane

a. Unsuccessful Attempt by Direct Hydrogenolysis of 2-(3,5-Dimethoxylphenyl)-3-methyloctanol-2 The carbinol used for these attempts was prepared from 2-(3,5-dimethoxybenzoyl)heptane and methylmagnesium bromide.

(a) 2-(3,5-Dimethoxyphenyl)-3-methyloctanol-2 (10 g) was mixed with 5 ml of hexane and 1 g of Girdler G-49A nickel-on-kieselguhr catalyst. This mixture was transferred to a 43-ml bomb, which was then inserted into a rocking autoclave. The mixture was heated to 100°C under 1500 psig hydrogen pressure for 3.5 hours. The mixture was removed from the bomb, catalyst and solvent were removed, and the residue was submitted for infrared spectrum. The spectrum was identical to that of starting carbinol.

(b) The process described in "a", above, was repeated. This time the temperature was maintained at 175°C under 2600 psig hydrogen pressure for 11 hours. There was no change in the infrared spectrum.

(c) The process was repeated at 250°C under 2500 psig hydrogen pressure for 2.5 hours, again with negative results.

(d) The process was repeated at 250°C under 2500 psig hydrogen pressure for 10 hours, also with negative results.

(e) An attempt utilizing Girdler G-13 copper chromite catalyst (1 g) was also unsuccessful. This time the mixture was heated to 250°C under 2500 psig hydrogen pressure for 4 hours.

(f) Finally, an attempt at low pressure hydrogenolysis was made. The carbinol (14 g, 0.05 mole) was dissolved in 50 ml of hexane. Adams' catalyst (platinum oxide, 0.05 g) was added, and hydrogenolysis was attempted at room temperature with 50 psig hydrogen pressure, in a Parr shaker. This attempt was also unsuccessful.

b. <u>Successful Reduction of Mixed 2-(3,5-Dimethoxyphenyl)-3-methyloctenes</u> A one-liter autoclave was charged with 25 g of 2-(3,5-dimethoxyphenyl)-3-methyloctenes-1 and -2 and 2.5 g of 65% nickel-on-kieselguhr (Girdler G-49A) in 100 ml of dry hexane together with 1750 psig of hydrogen. The temperature was gradually increased to 125°C. After three hours the pressure was increased to 2850 psig of hydrogen and maintained there for another 2.5 hours. After filtration and removal of the solvent, the residue, 24.8 g, was submitted for infrared and ultraviolet spectroscopy and VPC and was identified as 2-(3,5-dimethoxyphenyl)-3-methyloctane, λ_{max} 272 and 278 mμ and λ_{min} 247 mμ, in 94.1 area-% purity.

28. 2-(3,5-Dimethoxyphenyl)-3-methyloctanol-2

a. From 3-Methyloctanone-2 and 3,5-Dimethoxyphenylmagnesium Chloride A 500-ml flask equipped with a stirrer, thermometer, condenser with drying tube, dropping funnel, and nitrogen inlet tube was charged with 9.7 g (0.33 g-atom plus 20% excess) of magnesium turnings and flamed out under nitrogen. A solution of 57.3 g (0.33 mole) of 1-chloro-3,5-dimethoxybenzene in 72.1 g (1.0 mole) of freshly-distilled tetrahydrofuran was prepared, and about 10 ml was added to the magnesium. When 1.0 g of bromoethane was added as initiator, a vigorous reaction occurred, and the remainder of the tetrahydrofuran solution of 1-chloro-3,5-dimethoxybenzene was added dropwise in 20 minutes. The mixture was then heated at reflux (pot temperature 79-85°C) for 3.5 hours. At the end of this time only a small amount of magnesium remained.

After cooling to room temperature, a solution of 47.4 g (0.33 mole) of 3-methyloctanone-2 in 30 ml of tetrahydrofuran was added dropwise in 22 minutes while maintaining the temperature at 10° to 20°C. The reaction mixture was heated at 60°C for 2.0 hours. The reaction mixture was then hydrolyzed by the addition of a solution of 17.8 g (0.33 mole) of ammonium chloride in 54 ml of water over a period of ten minutes while keeping the temperature below 10°C. When the addition was complete, the mixture was stirred for 30 minutes and the precipitate allowed to settle out. The organic layer was separated by decantation and the residue was extracted with two 135-ml portions of diethyl ether. The solutions were com-

bined and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, 91.6 g of red-orange residue, assumed to be the desired 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2, was obtained. A 1.5 g sample was retained for study by VPC and the remainder was dehydrated as outlined below.

When the reaction was carried out on a larger scale, the aldol side-reaction was discovered. Details of the work-up and a discussion of the products appear above in section II.A.3.b.

Reactions where the tetrahydrofuran was displaced with dibutyl ether or diglyme were otherwise carried out as described in this section.

b. From 2-(3,5-Dimethoxybenzoyl)heptane and Methylmagnesium Bromide A 500 ml flask equipped with a stirrer, thermometer, condenser with drying tube, addition funnel, and nitrogen inlet was charged with 31 ml of a 3 M solution of methylmagnesium bromide in diethyl ether. Then a solution of 21.8 g (0.082 mole) of 2-(3,5-dimethoxybenzoyl)heptane in 30 ml of dry ether was added dropwise in 15 minutes while maintaining the temperature at 15-20°C. After heating at reflux for one hour, the mixture was hydrolyzed by pouring it onto a solution of 10 g of sulfuric acid in 100 ml of water and 200 cc of crushed ice. After stirring for 10 minutes another 10 ml of sulfuric acid was added and the mixture stirred for an additional half hour. The two layers were separated. The aqueous layer was extracted with two 100 ml portions of ether. The ethereal solutions were combined, washed and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, 21.6 g of pale yellow residue remained. VPC indicated this material to be greater than 95 area-% product, representing a 93% yield. Distillation gave

2-(3,5-dimethoxyphenyl)-3-methyloctanol-2, bp 134°C/0.23 mm, n_D^{20} 1.5100, greater than 97 area-% pure by VPC.

29. <u>2-(3,5-Dimethoxyphenyl)-3-methyloctenes</u>

a. <u>Dehydration with Oxalic Acid</u> Crude 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2, 90 g, and 45 g of anhydrous oxalic acid were placed in a flask and heated at 130-140°C for 1.7 hours. After cooling, 100 ml of benzene was added and the liquid was then separated by decantation. The solid was washed with another 100 ml of benzene. It was then dissclved in 250 ml of water and the resulting solution extracted with two 100 ml portions of benzene. All the benzene solutions were combined, washed until neutral, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, distillation gave 50.4 g of a fraction, bp 113-153°C/0.5- 0.65 mm (mostly 123-133°C). The yield of the <u>cis</u> and <u>trans</u> isomers of 2-(3,5-dimethoxyphenyl)-3-methyloctene-2 was 65% based on VPC. Redistillation resulted in the isolation of the desired product, bp 114-119°C/0.25 mm in greater than 95 area-% purity.

b. <u>Dehydration with Iodine</u> Crude 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2, 40.7 g, and 1.5 g (0.006 mole) of iodine were placed in a flask and heated at 99-103° for 40 minutes. At this point water could be observed condensing around the top of the flask. The mixture was cooled and transferred to a separatory funnel and 50 ml of benzene added. The mixture was then washed with two 25-ml portions of a 6% aqueous sodium thiosulfate solution followed by two 50-ml portions of water. The benzene solution was then heated with activated charcoal,

filtered hot, and the solvent removed. Distillation of the residue gave 7.4 g, bp up to 88°C/0.3 mm; 2.6 g, bp 94-115°C/0.3 mm; 19.8 g, bp 113.5-120°C/0.25 mm; and 6.4 g of residue. Examination by VPC indicated that the first fraction contained 25 area-% of 1-chloro-3,5-dimethoxybenzene and 25 area-% of 3-methyloctanone-2, but none of the desired product. The second fraction contained 49 area-% of 1-chloro-3,5-dimethoxybenzene together with 26 area-% of the cis- and trans-isomers of the desired 2-(3,5-dimethoxyphenyl)-3-methyloctene-2. The third fraction contained 76 area-% of the cis- and trans-isomers of the desired product. VPC also showed the 6.4 g residue to contain a considerable amount of product. The yield based on these VPC results was at least 46%.

The infrared spectrum of the third fraction compared well with that of an authentic sample of the 2-(3,5-dimethoxyphenyl)-3-methyloctene-2 supplied by the Chemical Corps. The ultraviolet spectrum of the third fraction was identical to that of the authentic sample.

30. Ethyl 2-Acetylheptanoate

A 1000-ml, round-bottomed flask was charged with 500 ml of absolute ethanol. Sodium metal, 23 g (1.0 mole), was cut into small pieces and added in portions to the alcohol while maintaining the temperature at 30-45°C. The mixture was stirred until all the sodium reacted. At this point 130.2 g (1.0 mole) of ethyl acetoacetate was added and the resulting solution was heated to 70°C and 166.3 g (1.0 mole) of 1-bromopentane was added dropwise at 70-75°C. The mixture was then heated at reflux for one hour and allowed to stand over the weekend.

After heating at reflux for two hours, the mixture was cooled and filtered. The solvent was removed by distillation at atmospheric pressure. The residue was distilled at reduced pressure, the keto-ester being collected at 83-86°C/1.0 mm. The yield was 130 g of crude product (92% pure by VPC) representing a yield of 59%. Literature[21] value for ethyl 2-acetylheptanoate: bp 116°C/10 mm, n_D^{25} 1.43261.

31. Ethyl 2-Acetyl-2-methylheptanoate

A 2000-ml, round-bottomed flask was charged with 400 ml of dry 2-methyl-2-butanol. Then 26.1 g (0.67 g-atom) of potassium metal was cut into small pieces and added portionwise at 60-70°C. When the addition was complete, stirring was continued until all the metal had reacted. To the resulting solution, 101 g (0.7 mole) of ethyl 2-methylacetoacetate was added and the mixture stirred for several minutes. Then 148.6 g (0.75 mole) of 1-iodopentane was added dropwise at 70°C in twenty minutes. The mixture was heated at reflux for three hours.

After cooling to room temperature, 300 ml of water was added and the mixture stirred. Although the mixture seemed to be neutral to pH paper, 10 ml of glacial acetic acid was added. The organic layer was separated, washed once with water, and allowed to dry over anhydrous magnesium sulfate.

After filtration, the solvent was removed by distillation at ambient pressure. Further distillation gave two major fractions: 9.4 g, bp 66°C/0.3 mm, shown by VPC to be 84.0 area-% product; and 101.2 g, bp 62-63°C/0.2 mm, shown by VPC to be 95.2 area-% product. The total yield of ethyl 2-acetyl-2-methylheptanoate, based on VPC, was 76%.

32. Attempted Meerwein Reaction (Ethyl 2-Amyl-3-(3,5-dimethoxyphenyl)-Crotonate)

A 500-ml round-bottomed flask was charged with 20 ml of concentrated hydrochloric acid, 20 ml of water, and 15.3 g (0.1 mole) of 3,5-dimethoxyaniline. This mixture was then stirred for 15 minutes, and 18.4 g (0.1 mole) of ethyl 2-ethylidene-heptanoate in 60 ml of acetone and 4 g of cupric chloride dihydrate in 10 ml of water were added under nitrogen. The resulting mixture was cooled to -4°C and a solution of 8 g (0.12 mole) of sodium nitrite in 20 ml of water added in 7 minutes at -5° to +5°C. The mixture was then allowed to warm up to room temperature. At 14°C nitrogen evolution started. After 45 minutes the temperature had reached 36°C and nitrogen was being evolved at a steady rate. The mixture was then heated at reflux (pot temperature 69°C) for 3 hours.

The mixture was extracted with two 125-ml portions of ether. The ether extracts were combined, washed with water until neutral, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, distillation gave only starting materials and a very small amount of high-boiling residue.

33. Attempted Reformatsky Reaction (Ethyl 2-Amyl-3-hydroxy-3-(3,5-dimethoxyphenyl)butyrate)

A 500-ml flask equipped with a stirrer, thermometer, condenser with drying tube, and a dropping funnel was charged with 19.6 g (0.3 mole) of 40-mesh metallic zinc that had been washed with dilute hydrochloric acid, ethanol, water, and acetone, and dried. Then,

about 40 ml of a solution of 48.6 g (0.27 mole) of 3,5-dimethoxyacetophenone and 57.6 g (0.25 mole) of ethyl 2-bromoheptanoate (Sapon Laboratories, redistilled) in 100 ml of dry benzene was run into the flask with stirring. There was no indication of reaction, so heating was initiated and addition was resumed. At 90°C there was a sudden, vigorous reflux, and the pot temperature increased sharply to 105°C. The addition was completed and the mixture was heated at reflux. In order to increase the pot temperature, solvent was removed by distillation. At a pot temperature of 130°C the residue, which had been becoming more and more viscous, solidified, probably because solvent removal left the halozinc salt of the hydroxyester. At this point, heating was discontinued, and 100 ml of benzene was added. The product was obtained by hydrolysis of the reaction mixture with 100 ml of 20% sulfuric acid. The organic layer was separated, washed with portions of 5% sulfuric acid, 10% aqueous sodium carbonate, and water, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, 75 g of a yellow liquid residue was obtained. Distillation gave 14 g of colorless liquid, bp 34-70°C/1.0 mm (mostly 35-36°C), 19 g of colorless liquid, bp 99-129°C/1.0 mm, which partially crystallized on standing, and 35 g of almost colorless liquid, bp 170-180°C/1.0 mm, as well as a small amount of residue. Redistillation of the high-boiling cut resulted in the recovery of the two lower-boiling materials and a much smaller amount of higher-boiling product. Apparently, decomposition was taking place.

According to the VPC, the mixture contained a high-boiling compound consistent with ethyl 2-amyl-3-hydroxy-3-(3,5-dimethoxyphenyl)butyrate; 3,5-dimethoxyacetophenone; and several other components. No ethyl 2-bromoheptanoate was present.

34. Ethyl 2-Ethylideneheptanoate

a. Attempted Dehydration of Ethyl 2-(1-Hydroxyethyl)heptanoate Using Dry Hydrogen Chloride Dehydration of ethyl 2-(1-hydroxyethyl)-heptanoate following the method of Natelson and Gottfried(60) was attempted. The method consists of passing dry hydrogen chloride through the hydroxy ester while heating on a steam bath. In this case, treatment for two hours in the manner outlined resulted in the recovery of unreacted ethyl 2-(1-hydroxyethyl)heptanoate.

b. Attempted Dehydration Using Iodine in Refluxing Benzene Dehydration of ethyl 2-(1-hydroxyethyl)heptanoate was attempted using the procedure of Hibbert(40). This consists of treatment of the β-hydroxyester with iodine in refluxing benzene. In this instance, after 16 hours of reflux, no reaction occurred and the starting material was recovered unchanged.

c. Attempted Dehydration Using Fused Potassium Acid Sulfate β-Hydroxyesters have been dehydrated by heating over fused potassium acid sulfate for several hours and this method has been studied extensively by Kon and Nargund(51). In the present work, heating ethyl 2-(1-hydroxyethyl)heptanoate over fused potassium acid sulfate for four hours at 130°-150°C resulted only in recovery of starting material.

d. Dehydration with Phosphorus Pentoxide Following the procedure of Doering and coworkers[25], a 500-ml flask equipped with a stirrer, thermometer, condenser, and addition funnel was charged with 11 g (0.075 mole) of phosphorus pentoxide in 25 ml of dry benzene. Then, 22.7 g (0.112 mole) of ethyl 2-(1-hydroxyethyl)heptanoate was added dropwise while the temperature was kept at 30°-40°C with occasional cooling. When the addition was completed, the mixture was heated to 75°C, cooled, and the solvent removed. Distillation of the residue gave a crude product, bp 56-63°C/0.3-0.7 mm. Redistillation resulted in the isolation of 14.6 g (71% yield) of a colorless liquid, bp 49-50°C/0.25 mm, n_D^{20} 1.4366. VPC showed the material to consist of essentially three components in 49, 12, and 39 area-%. Separation and investigation with infrared indicated that the 49 and 12 area-% peaks were cis-trans isomers of the desired α,β-unsaturated ester while the 39 area-% peak was the undesirable β,γ-unsaturated ester, ethyl 2-vinylheptanoate. Neither ester has been previously reported.

e. Dehydration with Phosphorus Oxychloride Following the method of Kon and Nargund[51], a 500-ml, round-bottomed flask was charged with 61.3 g (0.4 mole) of phosphorus oxychloride and 50.6 g (0.25 mole) of ethyl 2-(1-hydroxyethyl)heptanoate in 50 ml of dry benzene. The mixture was heated at reflux (pot temperature 95°C) for 22 hours. After removal of the solvent and unreacted phosphorus oxychloride, distillation resulted in the isolation of 30 g of crude product. Upon redistillation, 27 g (65% yield) of a colorless liquid, bp 45-46°C/0.2 mm, was obtained. Examination by VPC indicated that it consisted of a mixture of cis- and trans-α,β-unsaturated ester in 76 area-% and β,γ-unsaturated ester in 24 area-%.

f. Dehydration with Phosphorus Oxychloride in Pyridine A 2000-ml, round-bottomed flask was charged with 122.6 g (0.8 mole) of phosphorus oxychloride and 400 ml of dry pyridine, and 136.5 g (0.675 mole, 94 area-% pure by VPC) of ethyl 2-(1-hydroxyethyl)-heptanoate was added dropwise. The addition was started at 30°C, and by the end of the addition, the temperature had reached 84°C. The mixture was then heated to 120°C and maintained at 120 to 130°C for 1.5 hours. After cooling to 10°C, the mixture was filtered to remove the pyridine hydrochloride that had formed. Most of the excess pyridine was removed by distillation at atmospheric pressure.

The residue was transferred to a separatory funnel and extracted with 67% diethyl ether. The aqueous layer was extracted with two 250-ml portions of ether. The ethereal solutions were combined, washed with water, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, distillation gave 107.3 g of clear, colorless liquid, bp 44-54°C/0.23 mm. VPC showed the desired ethyl 2-ethylideneheptanoate to be present in 65.1 area-%. The undesired β,γ-unsaturated ester, ethyl 2-vinylheptanoate, was present in only 2.2 area-%. However, two components of slightly higher retention times were present in 20.5 and 12.2 area-%, respectively.

Although these components were not separated and identified, it was felt that they probably represented the two dl pairs of ethyl 2-(1-chloroethyl)heptanoate since pyridine and phosphorus oxychloride could readily replace hydroxyl with chlorine. A 500-ml flask was charged with 107 g of the mixture of esters and then 10 g (0.179 mole) of potassium hydroxide in 87 ml of anhydrous ethanol was added dropwise. The addition was started at 25°C and the temperature had reached 37°C by the end of the addition. The mixture was heated at 50°C for thirty minutes, cooled, filtered, and the solvent removed. Distillation of the residue gave 89.3 g of clear, colorless product, bp 46-47°C/0.23 mm, n_D^{20} 1.4422; calculated for $C_{11}H_{20}O_2$: C, 71.7; H, 10.9; found; C, 71.8; H, 10.9. VPC indicated the product to be ethyl 2-ethylideneheptanoate in 98.1 area-% purity. The yield, based on ethyl 2-(1-hydroxyethyl)heptanoate, was 76%.

35. Ethyl 2-(1-Hydroxyethyl)heptanoate

A 1-liter autoclave was charged with 99 g (0.49 mole) of ethyl 2-acetylheptanoate in 150 ml of ethanol and this solution was placed under 1450 psig of hydrogen and heated at 125°C for two hours using nickel-on-kieselguhr catalyst, following the procedure of Adkins and coworkers(7). When the hydrogenation was complete, the mixture was filtered to remove the catalyst. After removal of the solvent, distillation gave 93.6 g (94% yield) of ethyl 2-(1-hydroxyethyl)heptanoate, bp 74-75°C/0.2 mm, n_D^{20} 1.4346. The compound has not been previously reported.

36. 2-Heptanol

Into a 3-liter flask in an atmosphere of nitrogen was placed 1500 ml of 3N methylmagnesium bromide (4.6 moles) in ether (Arapahoe Chemicals, Inc., Boulder, Colorado). To the Grignard solution was added dropwise 226 g (2.3 moles) of hexanal in 500 ml of anhydrous ether in 85 minutes at a rate to maintain gentle reflux. The reaction mixture was heated under reflux for an additional hour and then hydrolyzed by pouring it onto 4000 g of ice and 200 ml of concentrated sulfuric acid. The ether layer was separated and washed twice with sodium bicarbonate solution. It was concentrated and the residue distilled yielding a clear, colorless fraction, bp 74-75°C/28 mm, weighing 228 g (87%).

37. 2-Methylheptanonitrile

A 1000-ml, round-bottomed flask fitted with a take-off stopcock on the bottom, was equipped with a stirrer, Dry Ice condenser with soda lime tube, thermometer, and addition funnel and charged with 500 ml of anhydrous liquid ammonia and 1.0 g of ferric nitrate nonahydrate. Then 2 to 3 g of sodium which had been cut into small pieces was added and air bubbled through the resulting solution until it was apparent that reaction was taking place. More sodium was then added portionwise until a total of 11.5 g (0.5 g-atom) had been added. The mixture was allowed to warm up to ammonia reflux and 27.6 g (0.5 mole) of propionitrile was added fairly rapidly. After stirring ten minutes the mixture was added dropwise (through the bottom take-off stopcock) to 53.3 g (0.5 mole) of 1-chloropentane which was in a flask equipped with a stirrer, thermometer, and Dry

Ice condenser with soda lime tube. When the addition was completed, the ammonia was allowed to evaporate. To the residue was added 200 ml of diethyl ether followed by 200 ml of water. The water was added cautiously at first until it was apparent that any unreacted sodamide had been decomposed. The two layers were separated and the aqueous layer was extracted with two 100 ml portions of ether. The ethereal solutions were combined, washed several times, and dried over anhydrous magnesium sulfate. After removal of the solvent, distillation gave 40 g (64% yield) of 2-methylheptanonitrile, bp 56°C/5.0 mm, n_D^{20} 1.4151 (literature[54] n_D^{20} 1.4154); calculated for $C_8H_{15}N$: C, 76.6; H, 12.1; N, 11.2; found: C, 76.6; H, 12.1; N, 11.0.

38. 3-Methyl-4-hydroxyoctanone-2

This preparation was carried out according to the method of Powell, Murray and Baldwin[66]. A 1-liter, 4-necked flask was equipped with stirrer, thermometer, Friederichs condenser, and 125-ml dropping funnel. The flask was charged with 90.4 g (1.254 moles) of butanone and 21 ml of 1N alcoholic potassium hydroxide solution. Stirring was started, and a slightly turbid, yellow solution resulted. Dropwise addition of 36 g (0.418 mole) of n-valeraldehyde was then carried out over a 30-minute period. The temperature of the mixture rose to 45°C during the course of the addition. The solution became orange-amber. The mixture was stirred for an additional half hour. Aqueous tartaric acid (1N, 27 ml) was then rapidly added over a 5-minute period. The precipitated tartrate was filtered off, and the small water layer in the

filtrate was discarded. The organic portion of the filtrate was dried over sodium sulfate. Excess butanone was then removed from the dried, brilliant yellow organic liquid by distillation at atmospheric pressure. The residue, weighing 49.4 g for a 75% crude yield, was then fractionated under reduced pressure. A significant forerun, believed to be 3-methyloctene-3-one-2 produced by thermally-induced dehydration, was taken, and then the product was collected at 64.5-65°C/0.75 mm, n_D^{20} 1.4429; reported[66,87] bp 98°C/16 mm, 73-76°C/1 mm, n_D^{29} 1.4404.

39. <u>3-Methyloctanol-2</u>

a. <u>From Acetaldehyde and 2-Heptylmagnesium Bromide *via* the Succinic Acid Half Ester</u>[1] The Grignard reagent was prepared from 146.9 g (0.82 mole) of 2-bromoheptane in 115 ml of anhydrous ether. This was then reacted with 33.0 g (0.75 mole) of acetaldehyde in 45 ml of anhydrous ether. Anhydrous dioxane (160 ml) was then added, followed by the addition of 75.1 g (0.75 mole) of succinic anhydride. After a few minutes had passed, the entire reaction mixture formed into a hard, solid mass. At this point an additional 500 ml of ether and 500 ml of dioxane was added. The solid mass soon softened, and efficient stirring was again possible. The mixture was refluxed at 52°C for one hour, then hydrolyzed by pouring onto cracked ice, followed by acidification with hydrochloric acid. The half-ester was isolated by ether extraction. The ether was removed under vacuum and the oily residue dissolved in a slight excess of 10% sodium hydroxide. The basic solution of the half-ester was then extracted with ether to remove neutral substances. The concentration of

sodium hydroxide was increased to 20%, and saponification was effected by refluxing the basic solution for about 4 hours. Ether extraction, followed by drying and distillation, gave the alcohol, bp 76°C/7.5 mm, n_D^{20} 1.4334.

This compound has been reported[1,66], bp 85-87°C/7 mm and 75°C/15 mm, n_D^{20} 1.4330 and n_D^{27} 1.437. The yield (based on VPC assay) was 43.2 g or 40%. The yield of crude alcohol (prior to distillation) was 61.5 g, or a crude yield of 57%, which agrees well with the 60% yield reported by Adams, Harfenist and Loewe[1].

Anal. Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.98. Found: C, 75.6; H, 13.8.

The sample chosen for elemental analysis was assayed by vapor phase chromatography and found to be 94.1% pure, having carbonyl and olefinic contaminants. Adams, Harfenist and Loewe(1) also report a high carbon analysis for their product.

b. <u>Avoiding the Use of Succinic Anhydride</u> A 1-liter flask equipped with a stirrer, thermometer, condenser with drying tube, dropping funnel, and nitrogen inlet tube, was charged with 38 g (1.57 g-atoms) of magensium turnings, and the entire system was flamed out under nitrogen. After cooling, 65 ml of anhydrous diethyl ether was added, and then a solution of 247.2 g (1.38 moles) of 2-bromoheptane in 125 ml of anhydrous ether containing a small crystal of iodine, was added dropwise at such a rate as to maintain reflux. By the end of the addition the temperature of the reaction mixture was 72°C. The mixture was then heated at reflux for one additional hour. After cooling the Grignard solution to -10°C, a solution of 55.1 g (1.25 moles) of freshly-distilled

acetaldehyde in 65 ml of anhydrous ether was added dropwise in one hour while maintaining the temperature at -5 to -15°C by means of a Dry Ice-methanol bath. The reaction mixture was then allowed to stand overnight.

The reaction mixture was hydrolyzed by the addition of a solution of 84.2 g of ammonium chloride in 240 ml of water while maintaining the temperature at 10°C or less. The organic layer was decanted off, and the solid residue was extracted with several portions of ether. The ethereal solutions were combined, washed with water, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, distillation gave the following fractions:

Boiling Range, °C	Press, mm Hg	Weight, g	n_D^{20}	Composition by VPC, Area-% 3-methyl-2-octanone	3-methyl-2-octanol
68-74	10-11	16.4	1.4230	68	24
74-78	9.7	15.9	1.4266	48	48
79-81	8.5-9.0	44.0	1.4430	9	85
Residue		25			

Literature values for 3-methyl-2-octanol are: 85-87°C/7.0 mm, n_D^{20} 1.4330(1); bp 75°C/15 mm, n_D^{27} 1.437(66).

40. 3-Methyloctanone-2

a. From 3-Methyloctene-3-one-2 The procedure chosen was that of Powell and Secoy(67). The dehydrated aldol, 70.1 g (0.50 mole) was dissolved in 200 ml of 95% ethanol. Platinum oxide, 0.8 g, was added and the mixture was reduced with hydrogen in a Parr reduction apparatus at 40 psig.

After filtration and removal of the solvent, distillation gave 39.7 g, bp 67-68.5°C/8.5 mm, n_D^{20} 1.4228; and 20.3 g, bp 68-70°C/8.3 mm, n_D^{20} 1.4268. VPC indicated that the lower-boiling cut was an approximately equimolar mixture of 3-methyl-2-octanone and an unknown compound.

The VPC of the higher-boiling cut showed 15 area-% 3-methyl-2-octanone, 65 area-% of the same unknown compound, and three minor components. Additional comments on these results appear in the discussion section II.A.3.a.(5).

b. <u>From 3-Methyloctanol-2[65]</u> 3-Methyloctanol-2 (31.5 g, 0.218 mole) was added, dropwise with stirring over a 1.3-hour period, to a solution of 27.1 g (0.091 mole) of sodium dichromate dihydrate and 49 g of concentrated sulfuric acid in 160 ml of water. The addition was exothermic, and the temperature was not allowed to exceed 30°C. After the addition had been completed, the mixture was stirred at room temperature for an additional 18 hours. The mixture was then extracted with ether, the extract being dried over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure leaving a pale-yellow liquid residue. This residue was distilled under reduced pressure, the ketone being collected from 66-68°C/13.5 mm, n_D^{20} 1.4195; reported[65] bp 64-65°C/18 mm, n_D^{27} 1.424. The yield of ketone, based on VPC assay, was 20.2 g or 65%.

<u>Anal</u>. Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.8. Found: C, 76.4; H, 12.8

c. <u>From Ethyl 2-Acetyl-2-methylheptanoate</u> A 1000 ml flask was charged with 74 ml of water, 370 ml of methanol, and 29.1 g (0.518 mole) of potassium hydroxide. Ethyl 2-acetyl-2-methylheptanoate, 85 g, (92 area-% pure) was added and the resulting solution was heated at reflux for four hours. Water, 40 ml, and 29.1 g of potassium hydroxide were added, and the mixture was then heated at reflux for another eight hours. Distillation at atmospheric pressure removed 390 ml of solvent. The residue was transferred to a one-liter separatory funnel and 92 ml of water was added. The resulting two layers were separated, and the aqueous layer was extracted with two 75-ml portions of ether. The extracts were combined with the organic layer, and the resulting solution was washed with three 100-ml portions of water and dried over anhydrous magnesium sulfate.

After removal of the solvent, distillation gave 33 g of 3-methyloctanone-2, bp 60-63°C/7-8 mm, n_D^{20} 1.4202, 97.9 area-% pure by VPC. The yield was 64%.

d. <u>From 2-Methylheptanonitrile</u> A 500-ml, round-bottomed flask was charged with 175 ml of a 3M methylmagnesium bromide solution in ether. The entire reaction was carried out under nitrogen. A solution of 62.6 g (0.5 mole) of 2-methylheptanonitrile in 60 ml of dry diethyl ether was added dropwise in 1.2 hours. The addition was started at 16°C, and by the end of the addition, the solution had come to a slow reflux at 35°C. The mixture was then heated at full reflux (40°C) for sixteen hours.

The reaction mixture was hydrolyzed by pouring onto crushed ice containing 250 g of 33% sulfuric acid. After stirring for one

hour, the two layers were separated. The ether layer was washed with water and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, a 30 g residue was obtained. This was much less than the expected amount.

Since some imines hydrolyze only slowly, it was felt that the low weight of residue might be due to incomplete hydrolysis. Therefore, 15 ml of concentrated sulfuric acid was added to the aqueous layer and it was allowed to stand overnight. After eighteen hours a second phase had formed. The aqueous mixture was extracted with three 100-ml portions of ether. The extracts were combined with the residue previously obtained and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, 60.3 g of yellow residue was obtained. Distillation gave 54 g of 3-methyloctanone-2, bp 64°C/9.5 mm, n_D^{20} 1.4195, 91% pure by infrared. The yield was 76%.

e. By the Amylation of Butanone

(1) Two-Flask Method A 1000-ml reaction flask fitted with a take-off stopcock on the bottom was charged with about 500 ml of anhydrous liquid ammonia and 1.0 g of ferric nitrate nonahydrate. Then 2 to 3 g of sodium that had been cut into small pieces was added and air bubbled through the resulting solution until it was apparent that reaction was taking place. More sodium was then added in portions until a total of 13.8 g (0.6 g-atom) of sodium had been added. The mixture was allowed to warm to ammonia reflux and 43.3 g (0.6 mole) of butanone was added fairly rapidly. After stirring the mixture five minutes, it was added dropwise

(through the bottom stopcock) to 75.6 g (0.5 mole) of 1-bromopentane, which was in a 500-ml, round-bottomed flask equipped with a stirrer, thermometer, and Dry Ice condenser with soda lime tube. When the addition was completed, the ammonia was allowed to evaporate. To the residue was added 200 ml of ether followed by 200 ml of water. The two layers were separated and the aqueous layer was extracted with two 100-ml portions of ether. The ethereal solutions were combined, washed several times, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled and everything boiling up to 61°C/4.0 mm was collected. This fraction, which weighed 30 g, was shown by VPC to be 86 area-% 3-methyloctanone-2 with no evidence of the other possible product, 3-nonanone. The yield was 36%.

(2) <u>One-Flask Method</u> A 1000 ml flask was charged with 500 ml of anhydrous ammonia and 1 g of ferric nitrate nonahydrate. A few small pieces of metallic sodium were added and air bubbled through the solution until it was apparent that reaction was taking place. Then more sodium was added portion-wise until a total of 13.8 g (0.6 g-atom) has been added. Butanone, 43.3 g (0.6 mole), was added dropwise in 5 minutes and the resulting mixture was allowed to stir for 10 minutes. 1-Bromopentane, 75.6 g (0.5 mole), was added dropwise in six minutes and the resulting mixture allowed to stir for one-half hour. The liquid ammonia was allowed to evaporate and 200 ml of ethyl ether was added followed by the cautious addition of 200 ml of water. The resulting two layers were separated and the aqueous layer was extracted with two 100 ml portions of ether. The ethereal solutions

were combined and washed with water until essentially neutral. After drying over anhydrous magnesium sulfate the ethereal solution was filtered and the solvent removed leaving 59 g of residue. Distillation gave three fractions: 2.0 g bp up to 47°C/5.4 mm, ca 50 area-% 3-methyloctanone-2; 36.0 g bp 52-55°C/5.3 mm, 5.5 area-% unknown low-boiler, 84.5 area-% 3-methyloctanone-2 and 8.4 area-% 3-nonanone; 14.7 g residue, 10 area-% 3-methyloctanone-2, 4 area-% 3-nonanone, and the remainder high-boiling. 3-Methyloctanone-2 was identified by its infrared spectrum and by VPC. The yield was 47% by VPC. 3-Nonanone was isolated by VPC in 92 area-% purity and identified by infrared spectrum and by comparison of the VPC with that of an authentic sample. The yield of this component was 6%, by VPC.

(3) <u>Using Excess Butanone and Sodium</u> The procedure outlined above in (2) was repeated using the following quantities of reagents: 1000 ml liquid ammonia, 1 g ferric nitrate nonahydrate, 23 g (1.0 g-atom) sodium, 72.1 g (1.0 mole) butanone, and 75.6 g (1.0 mole) 1-bromopentane. The weight of residue obtained was 64.7 g. Distillation gave three fractions: 1.1 g bp up to 55°C/7.5 mm, 45 area-% 3-methyloctanone-2; 45 g bp 57-61°C/6.5 mm, 6.3 area-% unknown low-boiler, 82.4 area-% 3-methyloctanone-2, and 8.2 area-% 3-nonanone; and 13.2 g residue bp above 61°/6.5 mm, 6 area-% 3-methyloctanone-2. The ketones were identified by VPC. The yield was 54% of 3-methyloctanone-2 and 5.2% 3-nonanone, by VPC.

(4) Using Amyl Chloride The above procedure was carried out twice using 53.3 g (0.5 mole) of 1-chloropentane in place of the 1-bromopentane. There was no appreciable product (>5%) formed in either experiment.

(5) Using Amyl Chloride and Sodium Bromide The following reactants were used in an amylation attempt following the procedure outlined in (2) above, except that 10.3 g (0.1 mole) of sodium bromide was added to the sodamide solution: 1000 ml liquid ammonia, 1 g ferric nitrate nonahydrate, 23 g sodium (1.0 g-atom), 72.1 g butanone (1.0 mole), and 53.6g(1.0 mole) 1-chloropentane. No significant amount of product was observed.

(6) Using Diamyl Sulfate The following reactants were used in an amylation attempt following the procedure outlined in (2) above: 1000 ml liquid ammonia, 0.3 g ferric nitrate nonahydrate, 23 g sodium (1 g-atom), 72.1 g butanone (1.0 mole), and 119.2 g diamyl sulfate (0.5 mole). The preparation of diamyl sulfate is described in section IV.10. The major product of the reaction was 3-methyl-octanone-2, 28 area-% by VPC, contaminated with 3-nonanone (8% yield by VPC) and with what was believed to be the two bimolecular ketols resulting from the self-condensation of butanone, together with their dehydration products.

(7) In Toluene Solvent A one-liter flask was equipped with Hershberg stirrer, thermometer, addition funnel, nitrogen inlet, and condenser topped with a soda-lime drying tube. The system was flamed out and allowed to cool under a stream of nitrogen. The flask was then charged with dry toluene (550 ml) and freshly cut sodium (12.9 g,

0.56 g-atom). The mixture was vigorously stirred and heated to reflux. After the sodium had been dispersed as a fine sand, freshly distilled t-amyl alcohol (48.5 g, 0.55 mole) was slowly added from a dropping funnel. The mixture turned pink during the 30 minute addition period. Heating at reflux was continued for 5.5 hours. The resultant clear yellow liquid was then cooled to room temperature and stored under dry nitrogen until used in the amylation.

A two-liter flask equipped with glass stirrer, thermometer, dry nitrogen inlet, addition funnel and condenser topped with soda-lime drying tube was flamed out and allowed to cool under a stream of dry nitrogen; then charged with 250 ml of dry toluene, butanone (36.0 g, 0.5 mole) and amyl bromide (90.6 g, 0.6 mole). The sodium t-amyloxide-toluene solution, previously prepared, was rapidly charged into the dropping funnel, then added dropwise to the rapidly-stirred reaction mixture. The addition was slightly exothermic, so an ice-water bath was intermittently placed in contact with the reaction flask. The color of the reaction mixture changed from water-white to yellow to orange during the 1-hour addition period. The mixture was then heated in an oil bath until the pot temperature reached 83°C. The color of the mixture intensified during the 0.75-hour heating period. The mixture was cooled to room temperature and hydrolyzed by the addition of 200 ml of water. The exothermic hydrolysis was moderated with an ice-water bath. The mixture was transferred to a separatory funnel, and the organic layer drawn off and set aside. The residual aqueous phase was then extracted with two 100 ml portions of ether. All organic phases were combined and washed with four 150 ml portions of saturated aqueous

sodium chloride solution. After drying over sodium sulfate, toluene was removed by distillation at atmospheric pressure. The residue was fractionated under reduced pressure. A series of six distillation cuts were collected from 35°C/23 mm to 127°C/14 mm, n_D^{20} 1.4396 - 1.4829. Instrumental evaluation indicated that the desired 3-methyloctanone-2 had been formed in only 2% yield, together with the usual contaminant 3-nonanone in 0.4% yield. About one-third of the starting amyl bromide was reclaimed unaltered. The major reaction products appeared to be α,β-unsaturated ketones, a pair lower boiling and a pair higher boiling than the desired ketone.

(8) In Ether Solvent The preparation of sodium t-amyloxide was as described above, except that the amount of dry toluene was diminished from 550 ml to 370 ml so as to prepare an approximately 1.5 M solution of the amyloxide.

A reaction system identical to that described for the amylation in toluene was dried in the usual manner, then charged with 370 ml of sodium dried ether and butanone (36.0 g, 0.5 mole). The sodium t-amyloxide solution was then slowly added from the dropping funnel. Amyl bromide (90.6 g, 0.6 mole) was then added dropwise to the turbid yellow reaction mixture over a 15 minute period. Stirring at room temperature was continued for 5 hours. The mixture was then hydrolyzed by the cautious addition of 200 ml of water. The hydrolysate was treated as previously described. Fractionation under reduced pressure provided a series of 5 cuts collected from 30°C/17 mm to 121°C/17 mm, n_D^{20} 1.4401 - 1.4808. Instrumental evaluation indicated that the desired 3-methyloctanone-2 had been formed in only 1% yield, along with a 0.3% yield of 3-nonanone. About one-third of the starting amyl bromide was re-

covered. The major reaction products again were found to be the same four α,β-unsaturated ketones formed when toluene had been used as exclusive reaction solvent.

f. Attempted Preparation from Epoxybutane

(1) Purification of 2,3-Epoxybutane The 2,3-epoxybutane used in the following series of experiments was obtained from Farchan Research Laboratories. The sample contained about 4% water, determined by Karl Fischer titration. Butylene oxides have been reported to form azeotropes with water at atmospheric pressure(99). The epoxide was shaken with an equal volume of dry n-octane. A water layer formed, and was drawn off and discarded. The turbid epoxide-octane solution was then dried for several hours over anhydrous magnesium sulfate, followed by a brief period in contact with Linde no. 4A molecular sieves. The solution was then slowly distilled through a short packed column to isolate the dry epoxide.

(2) Reaction of 2,3-Epoxybutane with Commercial n-Amyl Sodium (1:1) A carefully dried, three-necked, 2-liter flask equipped with a Hershberg tantalum stirrer, dry nitrogen inlet, thermometer, and drying tube was charged with amyl sodium (50 g, 0.532 mole) (supplied by Orgmet as a slurry in heptane). This operation was carried out in a dry box under a dry nitrogen atmosphere. A rapid flow of dry nitrogen was passed through the reaction system during subsequent reaction. The mixture was cooled to -20°C in a Dry Ice-kerosene bath. Freshly dried, 2,3-epoxybutane (36 g, 0.5 mole) dissolved in 70 ml of dry octane was added dropwise over a period of 1.7 hours. The cooling bath was removed shortly after the addition was begun,

since the reaction was not exothermic. The mixture was stirred at room temperature for 10 minutes, then again cooled to -20°C. Absolute ethanol, 100 ml, was added over a 20-minute period. The mixture thickened and then thinned again during the addition. Water, 200 ml, was rapidly added. Two layers formed, an upper water-white organic layer and a lower yellow aqueous layer. The aqueous layer was extracted with ether, and the ether extract combined with the original organic layer. The combined organic phases were washed with water and dried over sodium sulfate. Ether was removed on a rotary evaporator, and the bulk of the reaction solvents were then removed by distillation at atmospheric pressure. The residue, a pale yellow liquid weighing 31 g, was fractionated under reduced pressure. In addition to residual hydrocarbon solvents, a small amount of liquid, 2.0 g, was collected from 43-45°C/5mm, n_D^{20} 1.4155. VPC and infrared spectra indicated that this small cut consisted of 83.9 area-% of the desired 3-methyloctanol-2 (2% yield).

(3) <u>Reaction of n-Amyl Sodium, Prepared in-situ, with 2,3-Epoxybutane (1:2)</u> A three-necked, 2-liter Morton flask was equipped with high speed stirrer, Nichrome Hershberg whip, dropping funnel, dry nitrogen inlet, thermometer and air-cooled condenser topped with a drying tube. The system was flamed out and allowed to cool under a stream of dry nitrogen. Sodium spheres (23.0 g, 1.0 g-atom) were charged into the flask, together with 300 ml of dry, synthetic octane. The octane was heated to reflux; then the stirrer was adjusted to high speed for about 2 minutes. Heating was discontinued, and the fine sodium dispersion was cooled to -10°C in a Dry Ice-kerosene bath. Moderate stirring was maintained throughout

the subsequent procedure. Purified n-amyl chloride (53.3 g, 0.5 mole) dissolved in 500 ml of n-octane was added dropwise over a 30-minute period. The mixture was stirred at -5°C for 30 minutes, then allowed to come to room temperature.

2,3-Epoxybutane (72.1 g, 1.0 mole) dissolved in 70 ml of n-octane was added dropwise to the amyl sodium dispersion over a 40-minute period. The addition was moderately exothermic. The mixture was stirred for 1.75 hr at room temperature, then cooled to -10°C. Absolute ethanol, 100 ml, was added, followed by the addition of 200 ml of water. The mixture was acidified by the addition of 60 g of glacial acetic acid. The aqueous layer was extracted with ether. All organic phases were combined, washed with water, then dried over sodium sulfate. After the removal of solvents, the residue was distilled under reduced pressure. In addition to residual reaction solvents, a small cut, 5.2 g, bp 53-54°C/8 mm, n_D^{20} 1.4140, was collected. Instrumental evaluation indicated that this cut consisted of 82.4 area-% of the desired product (6% yield).

(4) Reaction of 2,3-Epoxybutane with Butyl Lithium A three-necked, 2-liter flask was equipped with stirrer, dropping funnel, dry nitrogen inlet, thermometer, syringe cap, and condenser topped with drying tube. The system was flamed out and allowed to cool under a stream of dry nitrogen. The flask was charged with butyl lithium (32.0 g, 0.50 mole) in hexane solution with a hypodermic syringe. Dry 2,3-epoxybutane (36.0 g, 0.5 mole) dissolved in 70 ml of dry n-octane was added dropwise over a two-hour period. After about

20 ml of the epoxide solution had been added with no apparent exotherm, the reaction mixture was heated to 50°C, heating was stopped, and the addition was continued. The reaction was self-sustaining, the temperature of the mixture rising to 60°C before the addition had been completed. The mixture was then gently refluxed for 45 minutes. After cooling the mixture to -10°C, 200 ml of water was slowly added. The mixture was acidified by the addition of 30 g of glacial acetic acid. The organic layer was separated and the residual aqueous layer extracted with ether. All organic phases were combined and washed with water, then dried over sodium sulfate. Solvent was removed and the residue distilled under reduced pressure. Several cuts were collected from 27-77°C/17 mm, n_D^{20} 1.3998-1.4238. Instrumental evaluation indicated that the desired product, 3-methylheptanol-2, had been formed in 6% yield. The best distillation cut assayed only 77 area-% purity by VPC.

The carbinol produced by the reaction was most probably the desired one, since its infrared spectrum exhibited absorption characteristic of a secondary alcohol, bonded -OH at 3350 cm^{-1}, and C-O bend at 1100 cm^{-1}. The nature and significance of other products formed during this reaction have been treated in the Discussion, section II.A.3.a.(6).

41. <u>3-Methyloctene-3-one-2</u>

3-Methyl-4-hydroxyoctanone-2 (q.v.) was prepared using 300 g (3.483 moles) of n-valeraldehyde. Excess butanone was removed, leaving a residue of 587.7 g. Iodine, 4.0 g, was added to this residue, and distillation continued at atmospheric pressure. Water was removed first and an unsaturated ketone distilled from 170-190°C/

760 mm. A large, dark-colored, viscous pot residue remained. The distillate was washed with two 100-ml portions of 2% aqueous sodium bisulfite solution and dried over calcium chloride. The crude unsaturated ketone, 201.6 g, was fractionated under reduced pressure and collected at 35-40°C/0.65 mm, n_D^{20} 1.4497-1.4512; reported[87] bp 55-60°C/1 mm. The yield of purified product was 164.8 g (34%, calculated as 3-methyloctene-3-one-2).

42. Attempted Preparation of Orcinol Monomethyl Ether by Basic Hydrolysis of 3-Methoxy-4-chlorotoluene

Following the procedure of Bottini and Roberts,[16] a 300-ml rocking autoclave was charged with 23.5 g (0.15 mole) of 3-methoxy-4-chlorotoluene and 175 ml of 4M sodium hydroxide solution. Heating was initiated. At approximately 340°C, the rocking mechanism was turned on. The pressure at this point was 2100 psig. The mixture was maintained at 340-350°C with rocking for two hours. The pressure at the end of this period was 2350 psig. After allowing it to cool overnight, the autoclave was vented. The contents were removed and acidified with 20% hydrochloric acid and then extracted with two 150-ml portions of ether. The extracts were combined, washed with water, and dried. After filtration and removal of the solvent, distillation gave 7.5 g (46% yield) of m-cresol, bp 49°C/0.6 mm, n_D^{20} 1.5384. The product had the same VPC retention time and infrared spectrum as an authentic sample of m-cresol.

43. 2-Phenyl-3-methyloctene-2

a. From Phenylmagnesium Bromide and 3-Methyloctanone-2

A 500-ml reaction flask was charged with 120 ml of 3 M phenylmagnesium bromide solution (Arapahoe) (ca. 0.36 mole) under

nitrogen. A solution of 47.4 g (0.33 mole) of 3-methyloctanone-2 in 50 ml of dry diethyl ether was added dropwise in 25 minutes while maintaining the temperature at 10-15°C. The mixture was then stirred at room temperature for 20 minutes and heated at reflux for one hour. After cooling, the mixture was poured onto ice and 300 ml of 25% sulfuric acid. After stirring 30 minutes, another 40 ml of concentrated sulfuric acid was added and stirring continued. The two layers were separated. The aqueous layer was extracted with three 100-ml portions of ether and then discarded. The ethereal solutions were combined, washed until neutral, and dried. The solvent was then removed under vacuum.

The residue was placed in a flask with two very small crystals of iodine and heated at 110-120°C for two hours. After cooling, the material was dissolved in twice its volume of ether and washed successively with three 100-ml portions of 30% sodium thiosulfate solution and two 100-ml portions of water. After drying and removal of the solvent, distillation gave 50 g of a fraction boiling at 73-78°C/0.25 mm, n_D^{20} 1.5069. VPC gave the following analysis:

Component	Retention Time, min.	Area-%
1	2.5	0.2
2	3.0	9.4
3	3.9	80.9
4	4.6	2.9
5	5.3	2.7
6	7.4	0.5
7	9.1	3.3

Component 3 was shown by infrared to be the terminal olefin, 2-phenyl-3-methyloctene-1. Component 2 was assumed to be one of the cis-trans isomers of the desired internal olefin, 2-phenyl-3-methyloctene-2. The other isomer could be component 4 or a part of 3.

b. Attempted Synthesis via a Phosphonate Carbanion A 500-ml reaction flask was charged with 36.3 g (0.15 mole) of pure diethyl 1-phenylethylphosphonate, 17.1 g (0.15 mole) of redistilled 2-heptanone, and 7.0 g of 51.8% sodium hydride (0.15 mole NaH) in 100 ml of anhydrous 1,2-dimethoxyethane and heating was initiated. At 70°C vigorous evolution of hydrogen started. The temperature was kept below 85°C until hydrogen evolution was over. By this time, a yellow precipitate had formed. The mixture was then heated at reflux for 80 minutes. After cooling the mixture to room temperature, 300 ml of water was added, slowly at first and then rapidly. The resulting mixture was extracted with three 150-ml portions of ether. The ethereal solutions were combined and washed with water until neutral and dried over anhydrous maghesium sulfate. After filtration and removal of the solvent, 33 g of pale amber residue was obtained. Distillation gave:

Cut	bp, °C/mm	Weight, g	n_D^{20}
1	up to 82/0.26	1	--
2	83-88/0.25	6.4	1.4675
3	92-110/0.2	5.4	1.4765
4	115-160/0.2	small	1.4755
5	residue	large	-

It was felt that only cuts 2 and/or 3 could be the desired olefin. Combination and distillation of 2 and 3 failed to yield a constant-boiling material. In addition, the refractive indices are too low to be the desired product.

This procedure was followed in a second run without success. In a third run, diglyme was used as solvent in order to obtain a higher reflux temperature but the results were still the same.

44. <u>Quaternary Phosphonium Bromide Preparation, General Procedure</u>

A 500-ml, round-bottomed flask equipped with a stirrer, thermometer, condenser with drying tube, and a nitrogen inlet, was charged with the desired amount of tertiary phosphine (usually 0.25 mole) and a slight excess (3 to 5%) of 2-bromoheptane. The mixture was then heated with stirring to the desired temperature range by means of an oil bath. The course of the reaction was followed by the formation of a second lower layer of phosphonium bromide. Heating was discontinued when the upper layer had essentially disappeared or the desired length of time had elapsed. The extent of reaction and of dehydrobromination was determined by removing the unreacted 2-bromoheptane and the heptene-1 and -2 by distillation at reduced pressure (ca 1.0 mm). The mixture of volatile materials obtained was then analyzed by VPC.

45. Resorcylation, General Procedures(52)

a. Two-Flask Method A three-necked, 2-liter flask (flask A) was equipped with stirrer, Dry Ice condenser topped with a soda lime tube and dropping funnel. A second one-liter flask fitted with a stopcock in the bottom (flask B) was arranged so that the stopcock could feed directly into flask A. Sufficient sodamide was prepared in flask A to convert the butanone to its carbanion. Excess sodamide (cf. Table V, section II. F. 2) was prepared in flask B. The butanone was added dropwise to the sodamide-liquid ammonia in flask A over a 15-minute period. The mixture was stirred an additional 15 minutes to insure conversion of the ketone to its sodium derivative. 1-Halo-2,4-dimethoxybenzene was then added dropwise as rapidly as liquid ammonia reflux would permit. Excess sodamide-liquid ammonia was run into flask A from flask B over a 20-30 minute period. The mixture was then stirred for the appropriate reaction time, followed by the addition of excess solid ammonium chloride. Ether, 250 ml, was added, and the ammonia allowed to boil off. The residue was poured onto a small quantity of cracked ice, and acidified by the addition of concentrated hydrochloric acid. The acidic mixture was extracted thoroughly with ether (extract I), the extract was washed with water and dried over sodium sulfate.

The remaining acidic aqueous phase was made basic by addition of solid sodium carbonate. This basic mixture was thoroughly extracted with ether (extract II), the extract washed with water, and dried over sodium sulfate.

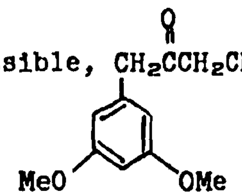
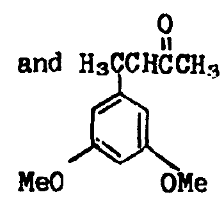
Ether was removed from extract I, and the residue distilled to yield butanone and its bimolecular condensation products, unreacted 1-halo-2,4-dimethoxybenzene, and higher-boiling cuts that contain varying amounts of the desired 3-(3,5-dimethoxyphenyl)-butanone-2 contaminated with 3,5-dimethoxyaniline. The desired ketone never formed in appreciable amounts; it was found in highest concentration in pot residues.

Ether was then removed from extract II; the residue was chiefly 3,5-dimethoxyaniline.

b. <u>One-Flask Method</u> This procedure was essentially the same as the two-flask method, except that required sodamide was prepared all at once in the same flask in which subsequent reaction was to take place.

c. <u>Isolation and Characterization of 3-(3,5-Dimethoxyphenyl)butanone-2</u> The pot residue that remained after the distillation of the residue from extract I, experiment No. 3, (Table V) was treated with semicarbazide hydrochloride according to the method of Shriner and Fuson(81). Crude semicarbazone was obtained which was recrystallized from aqueous ethanol, to yield tiny white needles, mp 176-178°C. The infrared spectrum of this semicarbazone was consistent with the desired structure, showing 1,3,5-substitution, methoxyl absorption and semicarbazone functions.

Elemental analysis: calc. for $C_{13}H_{19}O_3N_3$: C, 58.8; H, 7.2; N, 15.8; found: C, 58.4; H, 7.4; N, 15.9.

Since two ketones were possible,  and , it was necessary to show that the ketone from which the semicarbazone was made was in fact a methyl ketone. A small portion of the semicarbazone was treated with dilute hydrochloric acid to regenerate the original ketone. The hydrolysate was extracted with ether and the ether was then removed to provide several mg of ketone. A small portion was submitted for infrared spectrum. The spectrum was consistent with the desired product. An iodoform test was run on another portion of the ketone and found to be positive indicating the existence of a methyl ketone. The ketone melted from 58-60°C; reported[1], mp 62.5°C. VPC demonstrated that this same ketone was formed in experiments 1, 4, 5 and 6, in addition to experiment 3.

d. Use of Digylme Solvent Sodamide (1.25 moles) was prepared in liquid ammonia according to the usual procedure. Diglyme previously refluxed over and distilled from calcium hydride, 250 ml, was added and the liquid ammonia allowed to evaporate. Butanone (54.2 g, 0.75 mole) was added dropwise over a 10 minute period, followed by the addition of 1-chloro-2,4-dimethoxybenzene (43.2 g, 0.25 mole). The mixture was stirred for 30 minutes, then quenched by the addition of excess solid ammonium chloride (71.2 g, 1.33 moles). The

reaction mixture was poured over cracked ice, and acidified with concentrated hydrochloric acid. The acidic mixture was extracted thoroughly with ether (extract I), the extract washed with water and dried over sodium sulfate. The remaining acidic aqueous phase was made basic by the addition of solid sodium carbonate. This basic mixture was thoroughly extracted with ether (extract II), the extract washed with water and dried over sodium sulfate.

Ether was removed from extract I, and the residue fractionated under reduced pressure. The desired 3-(3,5-dimethoxyphenyl)butanone-2 was formed in only 3% yield (determined by VPC), 3,5-dimethoxyaniline was absent, and 71% of the starting halide was recovered. In addition to the desired ketone, apparently two other ketones were formed in trace amounts. Infrared spectra indicated these to be 1-(3,5-dimethoxyphenyl)butanone-2 and either 1-(2,4-dimethoxyphenyl)-butanone-2, or 3-(2,4-dimethoxyphenyl)butanone-2.

Ether was removed from extract II; the residue was mainly diglyme.

e. <u>Use of Lithium Alkyl Amides</u> A 2000 ml three-necked flask was equipped with stirrer, condenser topped with drying tube, dry nitrogen inlet and 500 ml pressure-equalizing dropping funnel topped with a syringe cap. The reaction system was flamed out and allowed to cool under a stream of dry nitrogen. The flask was then charged with 300 ml of anhydrous ether and dibutylamine (72.4 g, 0.56 mole). Butyllithium (32.0 g, 0.50 mole) in hydrocarbon solvent (supplied by the Foote Mineral Company as a 14.9 wt % solution) was introduced into the dropping funnel by means of a hypodermic syringe. Dropwise addition of the butyllithium solution required 1.2 hours. Butanone

(18.0 g, 0.25 mole) was then added, followed by the addition of 1-chloro-2,4-dimethoxybenzene (43.2 g, 0.25 mole). The mixture was refluxed for 3.7 hours, then cooled to room temperature and hydrolyzed by the cautious addition of 200 ml of water. The mixture was acidified with hydrochloric acid and thoroughly extracted with ether (extract I). The residual aqueous phase was then made basic and again extracted with ether (extract II). Both extracts were dried and distilled. Instrumental evaluation, including VPC and infrared, indicated the following to be among the reaction products recovered from extract I: unreacted 1-chloro-2,4-dimethoxybenzene (41% yield), the desired ketone [3-(3,5-dimethoxyphenyl)butanone-2] together with three isomeric ketones (5% total yield), a trace of what appeared to be 2,2',4,4'-tetramethoxybiphenyl (coupling product), and the major reaction product, apparently 3,5-dimethoxy-N,N-dibutylaniline (44% yield). This latter product is not a known compound; it was isolated in excellent purity as a brilliant pale yellow liquid: bp 139-140°C/ 0.70 mm, n_D^{20} 1.5233. Anal. Calc. for $C_{16}H_{27}O_2N$: C, 72.4; H, 10.3; N, 5.3. Found: C, 72.1; H, 10.3; N, 5.3. Dibutylamine was recovered from extract II.

B. SYNTHESIS OF 2-(3,5-DIHYDROXYPHENYL)-3,4-DIMETHYLOCTANE (II)

Compounds are arranged in alphabetical order.

1. 2-(3,5-Dihydroxyphenyl)-3,4-dimethyloctane (II)

2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctane was cleaved using the procedure described in section IV.A.19 and the following quantities: crude 2-(3,5-dimethoxyphenyl)-3,4-dimethyloctane, 18.9 g (0.068 mole); 48% hydrobromic acid, 58 ml; and glacial acetic acid, 180 ml.

Removal of the solvent from the ether extracts resulted in 16.9 g of higher-boiling material, which was distilled. VPC of the distillate showed 5.6 area-% low boilers, 23.1 area-% of what was assumed to be the monomethoxy compound, and 71.4 area-% of the desired resorcinol.

It was therefore necessary to recycle the mixed cleavage products. The desired product was finally isolated; 7.9 g, bp 160-161°C/ 0.3 mm.

<u>Anal</u>. for $C_{16}H_{26}O_2$: Cald. C, 76.75; H, 10.47. Found: C. 76.2; H, 10.3.

The VPC of the product, Figure 5, showed a principal component at a retention time of 4.8 min, 96.9 area-%, with other components totalling 3.1 area-% poorly resolved at retention times of about 3.0 min. The VPC was determined on an Aerograph Model A-350, 6 ft 15% Apiezon L on 30-60 mesh Chromosorb W, 265°C, 100 cc He/min.

The infrared spectrum of II, Figure 6, is consistent with the structure and free of absorptions attributable to the monohydroxymonomethoxy intermediate.

2. <u>2-(3,5-Dimethoxybenzoyl)-3-methylheptane</u>

3,5-Dimethoxyphenylmagnesium chloride was prepared in the usual manner from 9.5 g (0.43 g-atom) of magnesium and 69.1 g (0.4 mole) of 1-chloro-3,5-dimethoxybenzene using as solvent 86.5 g (1.2 moles) of anhydrous tetrahydrofuran containing a small crystal of iodine. It was then reacted with 59.9 g (0.43 mole) of 2,3-dimethylheptanonitrile and, after hydrolysis, distillation gave 58.8 g of 2-(3,5-dimethoxybenzoyl)-3-methylheptane, bp 138-142°C/0.25 mm, <u>ca</u> 90 area-% pure by VPC. Exact purity could not be determined by VPC due to the presence of diastereomers. The yield was 50%.

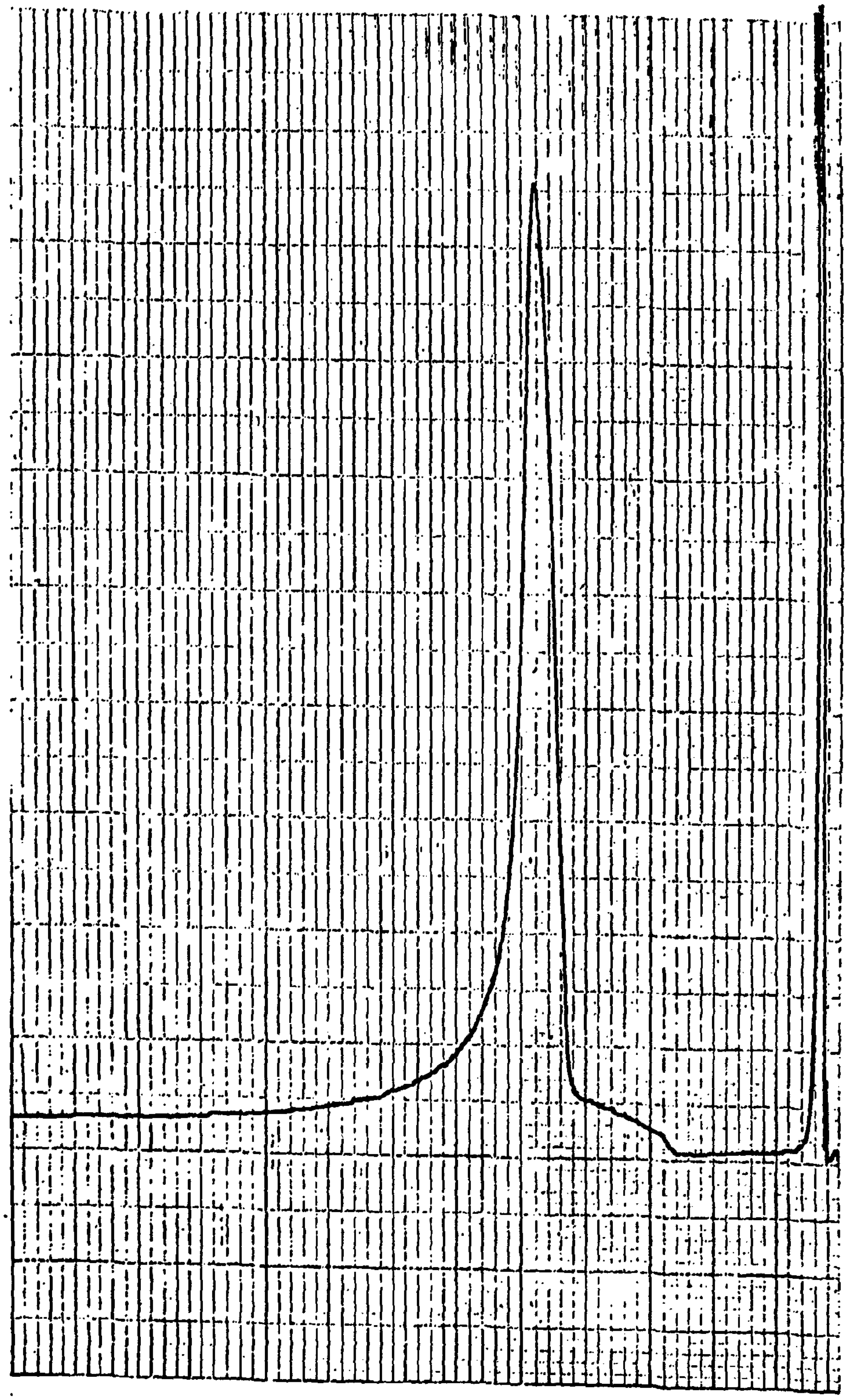


Figure 5. Vapor phase chromatogram of 2-(3,5-dihydroxyphenyl)-3,4 dimethyloctane, II.

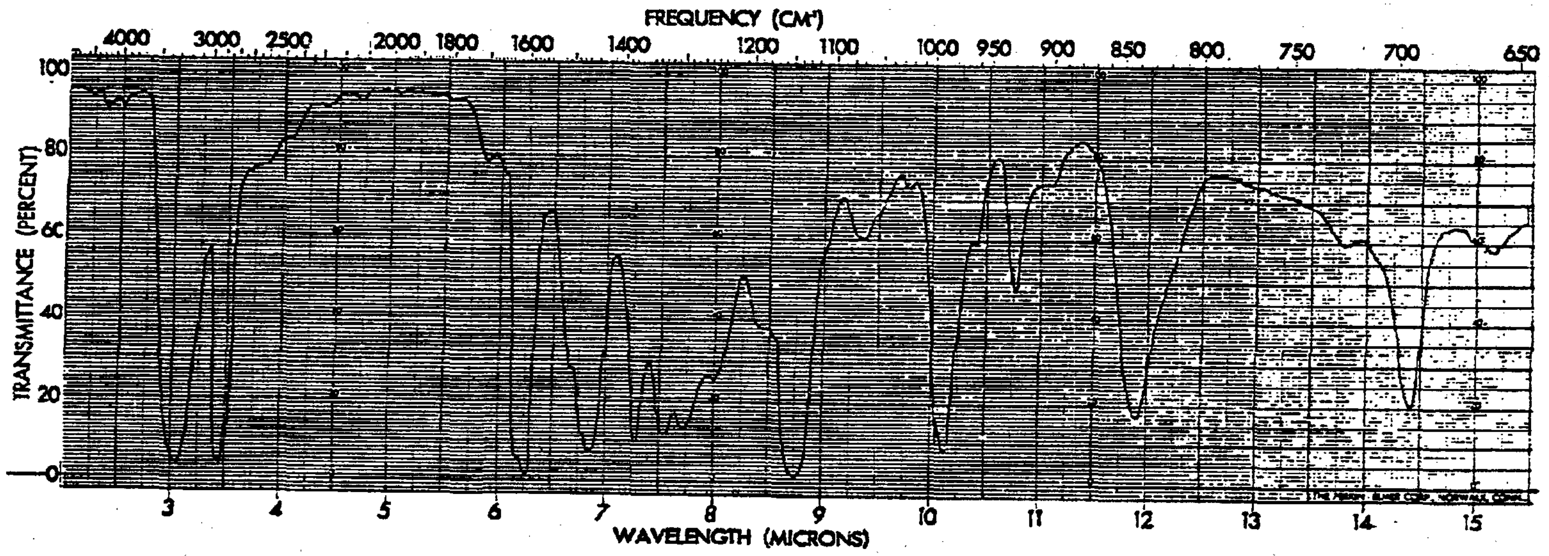


Figure 6. Infrared spectrum of 2-(3,5-dihydroxyphenyl)-3,4-dimethyloctane, II. Perkin-Elmer model 21 double beam spectrophotometer, liquid film, sodium chloride optics.

3. 2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctane

A one-liter autoclave was charged with 20 g of 2-(3,5-dimethoxyphenyl)-3,4-dimethyloctene-1, 100 ml of hexane, 2 g of 65% nickel-on-kieselguhr (Girdler G-49A), and 3000 psig of hydrogen. It was heated at 150°C for six hours, the mixture filtered from the spent catalyst, and the solvent removed to leave a residue that was not completely reduced. The procedure was repeated, using 4 g of catalyst. Completeness of reduction was verified by the use of ultraviolet, infrared and VPC analysis. No further purification was required.

4. 2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctene-1 via the Wittig Reaction

A 500 ml flask equipped as usual was charged with 64.2 g (0.18 mole) of methyl triphenylphosphonium bromide (Aldrich) in 150 ml of dry benzene. Then 104 ml of 14.9% (by wt.) of butyl lithium solution (Foote Mineral Co., active contents 11.6 g, 0.18 mole) was added dropwise in 75 minutes at 28-32°C. The color changed from white to deep orange. The resulting mixture was heated to 60°C and cooled. A solution of 49 g (0.176 mole) of 2-(3,5-dimethoxybenzoyl)-3-methylheptane in 40 ml of dry benzene was added, keeping the temperature below 40°C. The mixture was heated at reflux for two hours, cooled, and filtered to remove the triphenylphosphine oxide. After removal of the solvent, distillation gave: 2 g, bp up to 125°C/0.35 mm; 21.3 g, bp 126-128°C/0.35-0.41 mm; and 5.2 g, bp 128-129°C/0.4 mm.

Instrumental analysis disclosed that all three cuts were the desired product contaminated with small, varying amounts of the starting ketone. This was removed by careful fractionation after reduction. The yield by VPC was 53%.

5. 2-(3,5-Dimethoxyphenyl)-3,4-dimethyloctenes-1 and -2

The previously described 2-(3,5-dimethoxybenzoyl)-3-methylheptane, 58.8 g, ca 90 area-% pure, was reacted with 83.3 ml of a 3M methylmagnesium bromide solution in diethyl ether (Arapahoe). After hydrolysis, distillation gave two main fractions: 10 g, bp 139°C/0.24 mm and 32.6 g, bp 139-140°C/0.23 mm. These fractions were not subjected to an analytical study but instead were dehydrated using iodine as described in section IV.A.29.b. Distillation resulted in the isolation of 20.4 g of 2-(3,5-dimethoxyphenyl)-3,4-dimethyloctenes-1 and -2, bp 117-118°C/ 0.2 mm. The mixture showed four major components on the VPC. These were assumed to be the cis-trans isomers of the 2-octene and the expected two pairs of diastereomers of the 1-octene.

6. 2,3-Dimethylheptanonitrile

Following the procedure described in section IV.A.37 for the alkylation of nitriles, 82.6 g (1.5 moles) of propionitrile was reacted with 220.1 g (1.33 moles) of 2-bromohexane using a sodamide solution prepared from 34.5 g (1.5 g-atom) of sodium in 1200 ml of liquid ammonia as the base. Distillation resulted in the isolation of 22.3 g of unreacted 2-bromohexane and 88.1 g of 2,3-dimethylheptanonitrile, bp 59°C/3.0 mm, 97.1 area-% pure by VPC. The total yield was 57% (by VPC).

C. SYNTHESIS OF 2-(3,5-DIHYDROXYPHENYL)-3,3-DIMETHYLOCTANE (IV)

Compounds are arranged in alphabetical order.

1. 2-(3,5-Dihydroxyphenyl)-3,3-dimethyloctane (IV)

2-(3,5-Dihydroxyphenyl)-3,3-dimethyloctane was cleaved using the procedure described in section IV.A.19 and the following quantities:

2-(3,5-dimethoxyphenyl)-3,3-dimethyloctane, 28.7 g; hydrobromic acid, 92 ml; glacial acetic acid, 270 ml.

Distillation of the final residue resulted in the isolation of the desired product; 18.6 g, bp 154-155°C/0.18 mm.

Anal. for $C_{16}H_{26}O_2$: Calcd: C, 76.7; H, 10.4. Found: C, 76.9; H, 10.4.

The VPC of the product, Figure 7, showed a principal component at a retention time of 3.9 min, 97.3 area-% and another component(s) at 3.3 min, 2.7 area-%. It was determined on an Aerograph Model A-350, 6 ft 10% SE-30 methyl siloxane polymer on 30-60 mesh Chromosorb P, 235°C, 85 cc He/min.

The infrared spectrum of IV, Figure 8, is consistent with the structure.

2. 2-(3,5-Dimethoxybenzoyl)-2-methylheptane

3,5-Dimethoxyphenylmagnesium chloride was prepared in the usual manner from 9.5 g (0.43 g-atom) of magnesium and 69.1 g (0.4 mole) of 1-chloro-3,5-dimethoxybenzene using as solvent 86.5 g (1.2 moles) of anhydrous tetrahydrofuran containing a small crystal of iodine. It was then reacted with 59.9 g (0.43 mole) of 2,2-dimethylheptanonitrile and, after hydrolysis, distillation gave 57.8 g (71% yield) of 2-(3,5-dimethoxybenzoyl)-2-methylheptane, bp 134-136°C/0.19 mm. in greater than 98 area-% purity.

3. 2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctane

The reduction was carried out as described above in section IV.B.3, using 35 g of 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctene-1, 100 ml of hexane and 3.5 g of catalyst for the initial attempt and 7 g for the final reduction. Completeness of reduction was verified by infrared and VPC. No further purification was required.

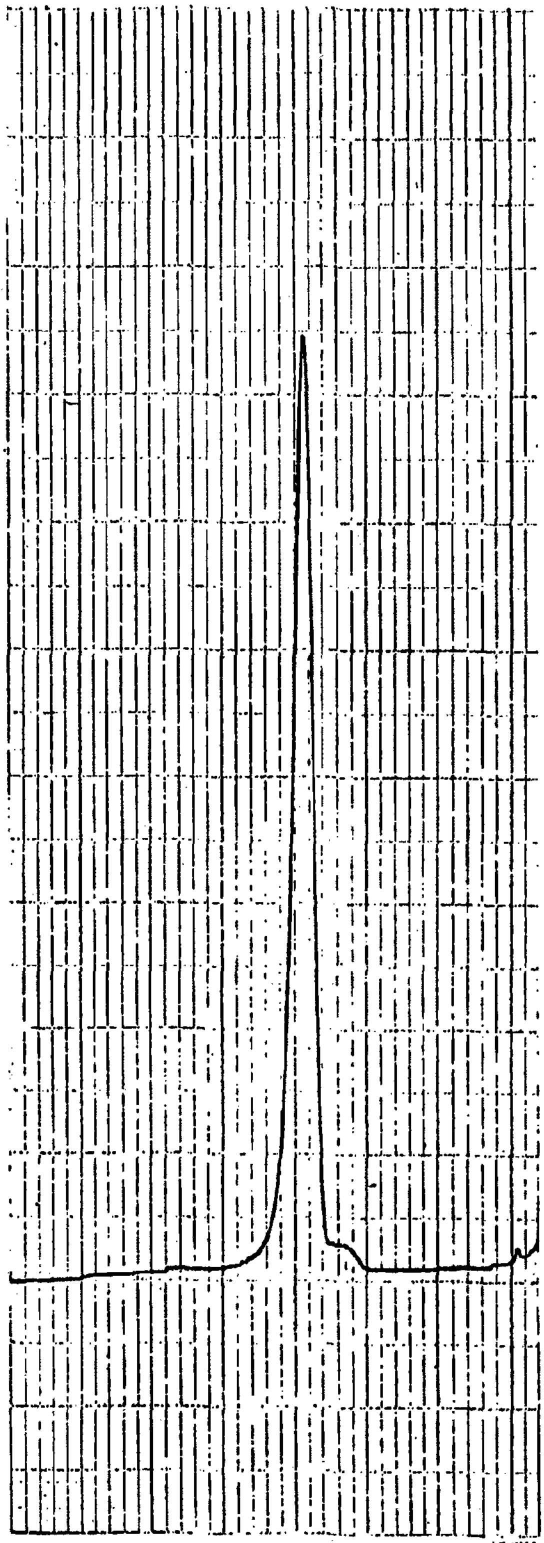


Figure 7. Vapor phase chromatogram of 2-(3,5-dihydroxyphenyl)-3,3-dimethyloctane, IV.

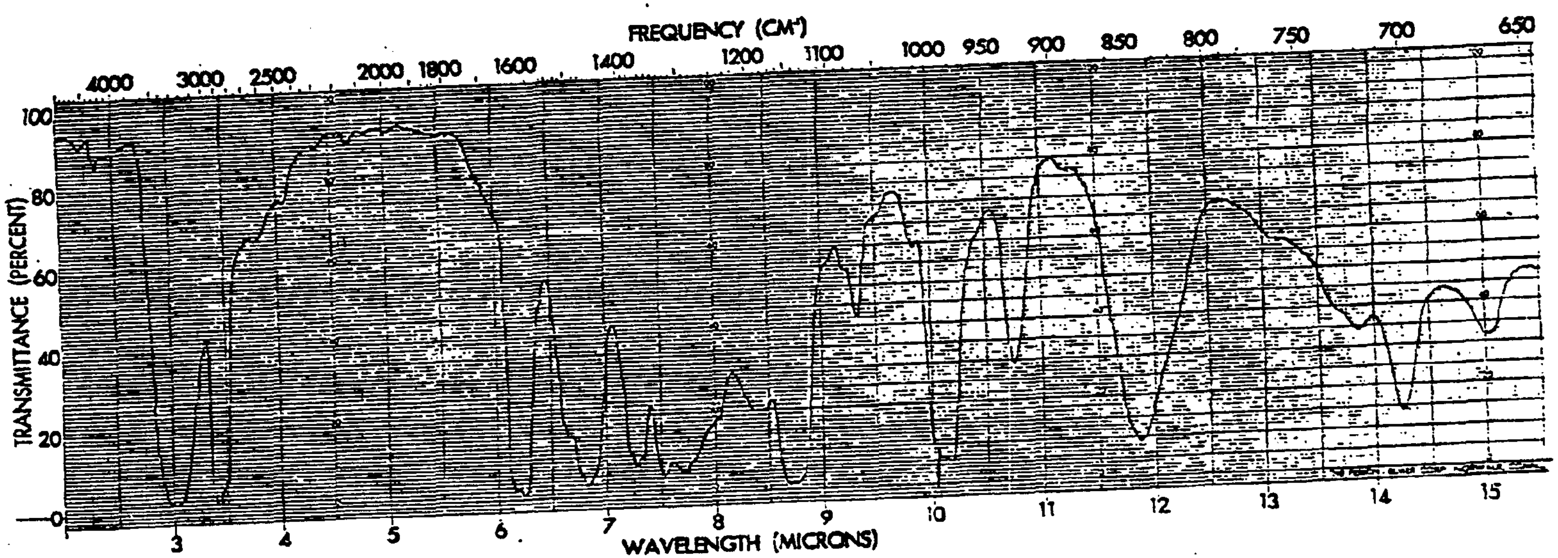


Figure 8. Infrared spectrum of 2-(3,5-dihydroxyphenyl)-3,3-dimethyloctane, IV. Perkin-Elmer model 21 double beam spectrophotometer, liquid film, sodium chloride optics.

4. <u>2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctanol-2</u>

2-(3,5-Dimethoxybenzoyl)-2-methylheptane, 56.3 g (0.202 mole), was reacted with 84 ml of a 3*M* methylmagnesium bromide solution in diethyl ether (Arapahoe). After hydrolysis, distillation gave 48 g (83% yield) of 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctanol-2, bp 139-140°C/0.15 mm which was not further characterized.

5. <u>Attempted Preparation of the Acetate of 2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctanol-2</u>

Crude 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctanol-2, 69 g, prepared as indicated above but not distilled, was placed in a flask with 400 ml of 1,2-dimethoxyethane and 50 g of pyridine. Then 50 g of acetyl chloride was added dropwise without cooling. The reaction mixture was heated at reflux for two hours and was allowed to stand overnight, after which 400 ml each of ether and water were added. The resulting two layers were separated and the organic layer was washed twice with water and dried on magnesium sulfate. After filtration and removal of the solvent, distillation was attempted. This resulted in decomposition as evidenced by continuous loss of vacuum and considerable fuming. A large amount of viscous residue was obtained together with several small distillation cuts, none of which had a constant boiling point.

6. <u>2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctene-1 via the Wittig Reaction</u>

The reaction was run exactly as the example in section IV.B.4 except that the following amounts were employed: methyl triphenyl phosphonium bromide (Aldrich), 89.3 g (0.25 mole); dry benzene, 400 ml; butyl lithium solution (Foote Mineral Co.) 143 ml (16 g, 0.25 mole); 2-(3,5-dimethoxybenzoyl)-2-methylheptane, 61.1 g

(0.22 mole) in 50 ml dry benzene. Distillation gave: 1.3 g, bp 113-116°C/0.25 mm; 36.4 g, bp 117-118°C/0.25 mm; and 6.5 g, bp 118-119°C/0.25 mm. Cut 1 was 90.9 area % product and 9 area-% of 8 other components. Cut 2 was 96 area-% product and 3.3 area-% starting ketone. Cut 3 was 92 area-% product and 8.0 area-% starting ketone. The yield by VPC was 68%.

7. 2-(3,5-Dimethoxyphenyl)-3,3-dimethyloctenes by Dehydration

A 44 g sample of 2-(3,5-dimethoxyphenyl)-3,3-dimethyloctanol-2 was dehydrated with iodine by the procedure described in section IV.A.29b. Distillation gave 29.4 g (80% yield) of a dehydration product, bp 115.5-116°C/0.2 mm. VPC indicated the presence of two major components, 78.1 area-% and 20.2 area-%.

8. 2,2-Dimethylheptanonitrile

Following the usual procedure for alkylation of nitriles, 103.7 g (1.5 moles) of isobutyronitrile were reacted with 142.2 g (1.33 moles) of n-amyl chloride using a sodamide solution prepared from 34.5 g (1.5 g-atom) of sodium and 1200 ml of liquid ammonia as base. Distillation resulted in the isolation of 85.8 g of 2,2-dimethylheptanonitrile, bp 59°C/4.0 mm, 97.2 area-% pure by VPC. The yield was 46%.

D. PRECURSORS OF 2-(3,5-DIHYDROXYPHENYL)-2,3-DIMETHYLOCTANE (III), 2-(3,5-DIHYDROXYPHENYL)-2-METHYLHEXANE (VI), AND 2-(3,5-DIHYDROXYPHENYL-2-METHYLHEPTANE (VII)

Compounds are arranged in alphabetical order.

1. 3,5-Dimethoxybenzyl Chloride via 3,5-Dimethoxybenzyl Alcohol

A 2-liter flask equipped as usual was charged with 1.3 moles (49.2 g) of lithium aluminum hydride in 1400 ml of dry diethyl ether and 1.4 moles (294.3 g) of ethyl 3,5-dimethoxybenzoate were added

dropwise at such a rate as to maintain gentle reflux. The time of addition was 5.5 hours. In the same manner 1.4 moles of ethyl acetate were added to destroy the unreacted lithium aluminum hydride. The semisolid reaction mixture was then hydrolyzed by portion-wise addition to six liters of crushed ice containing 300 ml of concentrated sulfuric acid. The resulting two layers were separated and the aqueous layer was extracted with several portions of ether. The ethereal solutions were combined, washed until neutral, and dried over magnesium sulfate. Filtration and removal of the solvent resulted in the isolation of 205.9 g (88% yield) of 3,5-dimethoxybenzyl alcohol as fine, slightly yellow needles.

This alcohol was not further purified but was dissolved in 600 ml of diethyl ether containing 15 ml of pyridine, and 2.4 moles (288 g) of thionyl chloride in 350 ml of ether were added dropwise at reflux using cooling as required. When addition was over, the mixture was stirred for 0.5 hour and then one liter of water was added cautiously. The ethereal layer was washed until essentially neutral and then dried over magnesium sulfate. After filtration and removal of the solvent distillation gave 181 g (80% yield) of 3,5-dimethoxybenzyl chloride, bp 101-102°C/ 0.55 mm. The product solidified on standing.

2. 3,5-Dimethoxybenzyl Cyanide

A flask was charged with 169 g (0.906 moles) of 3,5-dimethoxybenzyl chloride, 73.5 g (1.5 moles) of sodium cyanide, 600 ml of 95% ethanol and 250 ml of water. The mixture was then refluxed for eighteen hours. The mixture was then partitioned between 500 ml of water and one liter of ether. The ethereal layer was separated, washed, and dried.

After filtration and removal of the solvent, 150.8 g (93.5% yield) of slightly yellow product were obtained. The product was purified by distillation to yield colorless 3,5-dimethoxybenzyl cyanide, bp 122-124°C/0.5-0.6 mm.

3. <u>Attempted Preparation of 2-(3,5-Dimethoxyphenyl)-2-methylheptane by Wolff-Kishner Reduction</u>

A dry, three-necked, 500-ml flask was equipped with glass stirrer, thermometer, dropping funnel, dry nitrogen inlet and an efficient reflux condenser topped with a drying tube. The flask was charged with 2.8 g of sodium and 140 ml of freshly distilled diethylene glycol. This mixture was heated under dry nitrogen to 180°C. Anhydrous hydrazine, 11.1 g (0.346 mole), was combined with 5 g of sodium hydroxide pellets in a separate flask. The hydrazine was refluxed over the sodium hydroxide for 30 minutes, then distilled directly into the dropping funnel attached to the flask containing the diethylene glycol-sodium mixture. Rigid precautions were taken to exclude air and moisture from the entire reaction system. The hydrazine was added to the diethylene glycol-sodium mixture over a 10-minute period. The mixture was cooled to room temperature, and 2-(3,5-dimethoxyphenyl)-2-methylheptanone-3 (14.8 g, 0.056 mole) was rapidly added. The mixture was refluxed overnight and cooled to room temperature. The reflux condenser was replaced with a simple distillation assembly, and excess hydrazine was distilled out of the system until the pot temperature rose to 210°C. The mixture was refluxed at this temperature for 24 hours, then cooled and poured onto a mixture of cracked ice and water. A brittle orange solid adhered to the

walls of the reaction flask and was insoluble in water, benzene, and ether. The mixture was extracted with benzene, and the benzene extract thoroughly washed with water and dried over sodium sulfate. Solvent was removed under reduced pressure leaving 7.8 g of a brown oily residue. This was fractionated under reduced pressure and, after collecting a small foreun, yielded an amber, viscous liquid, bp 138-141°C/0.40 mm; n_D^{20} 1.5252. Instrumental evaluation indicated that this liquid was not the expected product, but was 2-(3,5-dihydroxyphenyl)-heptanone-3. VPC indicated that this product of ether cleavage had been produced in 29% yield.

4. <u>2-(3,5-Dimethoxyphenyl)-2-methylheptanone-3</u>

This procedure is essentially that used by Adams, MacKenzie and Loewe(5) to prepare 2-(3,5-dimethoxyphenyl)-2-methylpentanone-3 and 2-(3,5-dimethoxyphenyl)-2-methyloctanone-3 from 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile and the appropriate Grignard reagent.

A one-liter flask was equipped with stirrer, dropping funnel, dry nitrogen inlet, thermometer and condenser topped with drying tube. The system was flamed out and allowed to cool under a stream of dry nitrogen. The flask was charged with 102 ml of 3M butylmagnesium chloride solution in ether (0.306 mole) (Arapahoe). 2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile, 21 g (0.102 mole), dissolved in 100 ml of dry ether, was added dropwise over a period of 30 minutes. The bulk of the ether was removed from the system by distillation, being simultaneously replaced with 250 ml of dry benzene. The mixture was refluxed for 48 hours, cooled in an ice bath, and 108 ml of 5N sulfuric acid was cautiously added. The bulk of the benzene was removed

from the hydrolysate by distillation. The dark brown residue, consisting of intermediate imine and sulfuric acid, was heated on a steam bath for 2 hours to promote the conversion of imine to desired ketone. The mixture was diluted with 200 ml of water and thoroughly extracted with ether. The ether extracts were combined and washed with water, and finally dried over sodium sulfate. Solvent was removed under reduced pressure leaving 26.9 g of a syrupy residue, which was distilled to provide the following cuts:

cut no.	bp, °C/0.65 mm	n_D^{20}	wt, g	area-% desired ketone, VPC
1	to 118	1.4967	2.2	20
2	117-119	1.5096	8.2	87
3	119-120	1.5095	4.3	94
4	120-122	1.5114	2.8	99
5	122-130	1.5135	1.7	88
pot residue			3.4	

In addition to expected bands, the infrared spectrum of the purest cut (cut 4) exhibited a weak absorption band in the N-H (O-H) region, indicating the presence of traces of either intermediate imine or the Grignard reduction product of the desired ketone (viz., the corresponding carbinol). The yield of 2-(3,5-dimethoxyphenyl)-2-methylheptanone-3 (based on VPC and disregarding pot residue) was 59%. This is a new compound.

Anal. for $C_{16}H_{24}O_3$: Calc. C, 72.7; H, 9.2; Found: C, 73.1; H, 9.3.

5. 2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile

a. From 3,5-Dimethoxybenzyl Cyanide, First Experiment Sodamide was prepared in the usual manner from sodium (14.0 g, 0.608 g-atom); liquid ammonia, 800 ml; and 0. 3 g of ferric nitrate nonahydrate. About two-thirds of the ammonia was allowed to boil off, then 800 ml of anhydrous ether was added and the mixture stirred until the bulk of the ammonia had been displaced. Dry nitrogen was circulated through the system during subsequent reaction. 3,5-Dimethoxybenzyl cyanide (100 g, 0.564 mole) slurried in 550 ml of dry ether was rapidly added and the mixture refluxed for 18 hours. The mixture was cooled to room temperature and freshly distilled methyl iodide (99.9 g, 0.704 mole) added dropwise over a 20 minute period. The mixture was refluxed for 2 hours, again cooled to room temperature and 200 ml of absolute ethanol added. The clear orange organic phase was decanted from the solid material present and washed thoroughly with water, the washings being added to the residual solids in the reaction flask. This aqueous solution was then extracted with ether, the ether extract washed with water then combined with the original organic phase. The dried extract was concentrated under reduced pressure. The orange oily residue weighed 103 g. This orange oil was dissolved in 250 ml of dry benzene, then about 200 ml of the benzene was removed by distillation at atmospheric pressure in order to azeotrope out any residual water present in the orange oil. The residue was again subjected to methylation using the same procedure. There was obtained 107 g of crude reaction product. This was fractionated under reduced pressure to provide three cuts:

wt, g	bp, °C	press, mm	n_D^{20}	Composition in area-%, by VPC monomethyl	dimethyl
5.2	74-127	0.45	1.5137	3.8	40.8
64.5	124-5.5	0.35	1.5196	12.7	85
19.6	127-9	0.30	1.5207	22.7	75.8
7.9	pot residue				

The infrared spectrum of the pot residue exhibited N-H absorption. The distinction between the mono- and dimethylated dimethoxybenzyl cyanides was made by trapping the individual components by VPC and determining their infrared spectra. The starting material, 3,5-dimethoxybenzyl cyanide, had an average retention time of 9.9 min; the monomethylated nitrile 9.1 min, and the dimethylated nitrile 8.1 min. The component having the lowest retention time, 8.1 min, had an infrared spectrum which differed from the spectrum of the 9.1 min component by exhibiting stronger 2963 cm^{-1} absorption (C-H stretching) and also exhibited absorption at 1387 and 1366 cm^{-1}, characteristic of $-C(CH_3)_2$. The 9.1 min component showed only weak 1377 cm^{-1} absorption, characteristic of $-C-CH_3$ absorption. Based on infrared spectra it would appear then that the major reaction product was the desired one. The yields of respective products, based on VPC, were 62% and 12% for the di- and monomethylated nitriles.

Since the di- and monomethylated nitriles could not be separated by distillation it was necessary to recycle the mixture. The remainder of the two best distillation cuts (61.9 g of the second

fraction and 15.6 g of the third fraction) were combined and again treated with methyl iodide (a large excess: 150 g, 1.063 moles) after preliminary treatment with 0.608 mole of sodamide. Distillation of the crude reaction product provided four cuts:

wt, g	bp, °C	press, mm	n_D^{20}	Composition in area-%, VPC dimethyl
2.7	87-121.5	0.75	1.5116	0.8
2.5	126.5-41.5	0.80	1.5158	40.8
29.0	141.5-2	0.80	1.5202	98.3
3.3	144-6.5	0.80	1.5238	95.6
7.9	pot residue, viscous tar			

An elemental analysis was obtained for the 29.0 g fraction, the purest sample of 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile. Calculated, for $C_{12}H_{15}O_2N$: C, 70.2; H, 7.4; N, 6.8. Found: C, 70.4; H, 7.4; N, 6.9.

b. Second experiment The procedure of the first experiment was used, with the following modifications: The concentration of reactants was varied. 3,5-Dimethoxybenzyl cyanide (113.2 g, 0.639 mole) was treated with 0.703 mole of sodamide, then subsequently with methyl iodide (136.1 g, 0.959 mole). The reflux period, after the methyl iodide addition, was increased from two to three hours. After work-up and isolation of the crude reaction product, it was again subjected to the methylation procedure just described. Removal of solvent left 128.4 g of a red-amber oil which was fractionated through a short, glass helix-packed column to give the following distillation cuts:

wt, g	bp, °C/0.70 mm	n_D^{20}	Composition in area-%, VPC monomethyl	dimethyl
9.8	86-118	1.5051	8.7	48.9
30.8	118.5-20.5	1.5201	18.1	78.1
40.4	121-4.5	1.5204	22.9	77.1
13.3	124-5	1.5213	33.1	66.4
3.3	125-7.5	1.5225	52.1	46.9
20.2	pot residue, viscous tar			

Based on the VPC, the yields of the two nitriles would be 54% of the dimethylated nitrile and 18% of the monomethylated nitrile.

c. <u>Attempted Preparation from Isobutyronitrile</u> Sodamide was prepared in the usual manner from sodium (23.0 g, 1.0 g-atom), ferric nitrate nonahydrate (0.3 g) and 800 ml of liquid ammonia. Isobutyronitrile (34.6 g, 0.5 mole) was then added over a 10 minute period, followed by stirring for 15 minutes. 1-Chloro-2,4-dimethoxybenzene (43.2 g, 0.25 mole) was then added over a 10 minute period, followed by stirring for 22 minutes. The reaction was quenched by the addition of solid ammonium chloride (66.9 g, 1.25 moles). The mixture was then poured onto cracked ice and acidified with concentrated hydrochloric acid, and extracted thoroughly with ether (extract I). The residual acidic aqueous phase was made basic by the addition of solid sodium carbonate, and again extracted with ether (extract II). Both extracts were dried over sodium sulfate. After removal of solvent under reduced pressure extract I left a residue of 28.6 g, and extract II a residue of 12.6 g. The residue from extract I was fractionated under reduced pressure to provide a series of three cuts, bp 48-81°C/0.75 mm; n_D^{20} 1.4982 - 1.5436. Instrumental evaluation indicated the distillate to be largely 1-chloro-2,4-dimethoxybenzene. Extract II was principally 3,5-dimethoxyaniline.

6. Ethyl 3,5-Dimethoxybenzoate

A flask was charged with 584 g (3.2 moles) of 3,5-dimethoxybenzoic acid, 1100 ml of absolute ethanol, and 120 ml of concentrated sulfuric acid. The mixture was then heated to gentle reflux for twenty hours, after which 800 ml of ethanol were removed by distillation at ambient pressure. The residue was partitioned between ether and water. The resulting layers were separated and the aqueous layer discarded. The ethereal layer was washed with two portions of water and was then extracted with three portions of 10% sodium bicarbonate. Neutralization of this extract resulted in the isolation of 25.8 g of unreacted acid. The ethereal solution was dried over magnesium sulfate, filtered, and the solvent removed. Distillation of the residue gave 568 g (88% yield) of ethyl 3,5-dimethoxybenzoate, bp 100°C/0.2 mm.

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Contracts DA-18-108-405-CML-807 and DA-18-108-CML-6632
CP-0-405-14419

A number of synthetic routes to 2-(3,5-dihydroxyphenyl)-3-methyloctane have been investigated. The most practical route starts from 1,3,5-trichlorobenzene, which is converted in two steps to 3,5-dimethoxyphenylmagnesium chloride. This Grignard reagent is reacted with 2-methylheptanonitrile, and the resulting ketone is reacted with methylmagnesium halide to give 2-(3,5-dimethoxyphenyl)-3-methyloctanol-2. This carbinol is dehydrated, reduced, and cleaved to produce the desired resorcinol.

A large number of other routes and variations in individual steps were also investigated
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3. Wittig Reaction
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and detailed comparisons of their merits are included.

The synthesis of six related alkylresorcinols was also investigated. Two of these were prepared: 2-(3,5-dihydroxyphenyl)-3,4-dimethyloctane and 2-(3,5-dihydroxyphenyl)-3,3-dimethyloctane. A key precursor for three of the others was prepared.

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